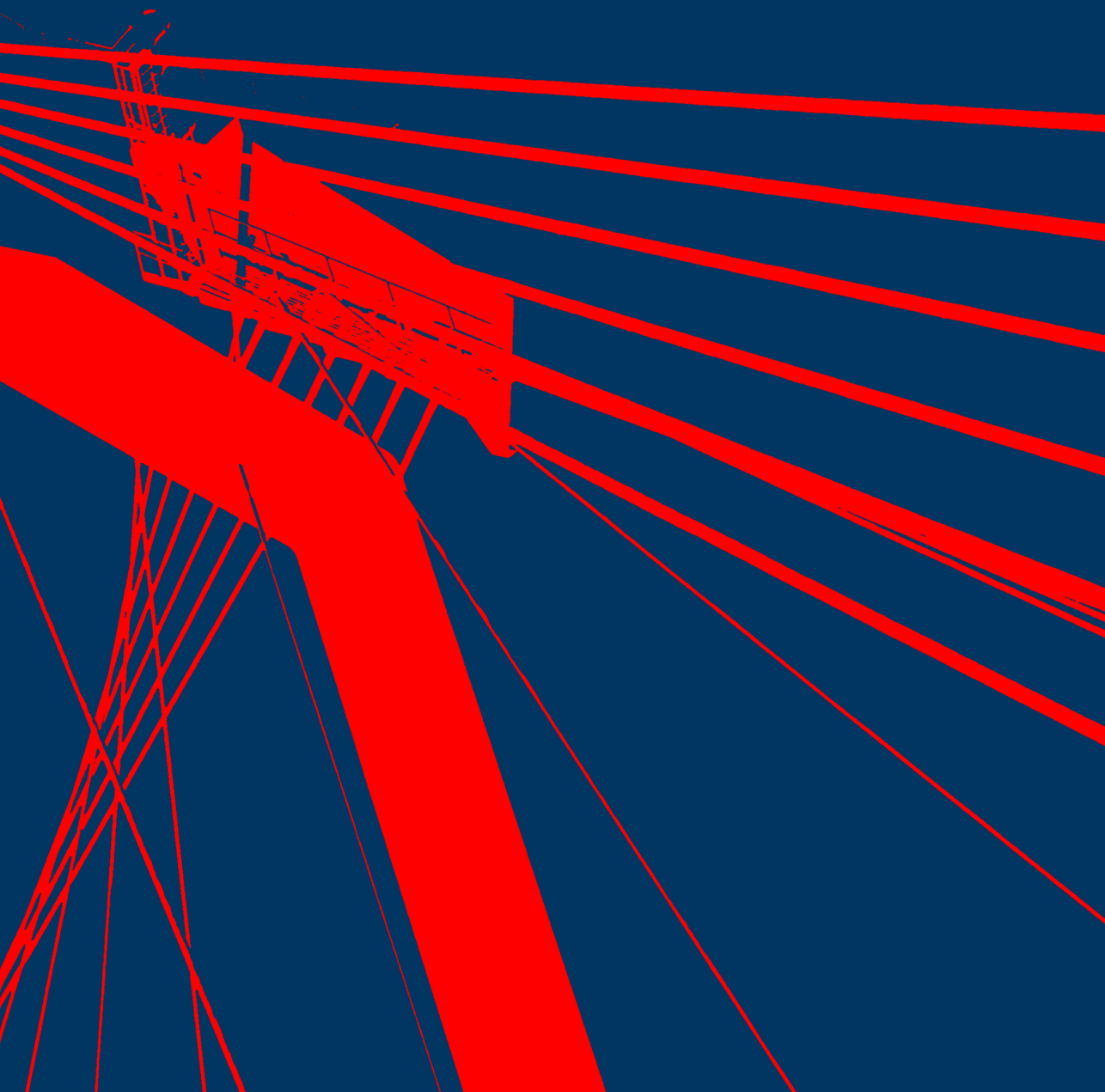
Transcatheter Aortic Valve Implantation: Current Results, Insights & Future Challenges

Rutger-Jan Nuis



Transcatheter Aortic Valve Implantation:
Current Results, Insights & Future Challenges

Rutger-Jan Nuis

ISBN: 978-94-6169-398-3

Cover “Willemsbrug Rotterdam” designed by Roderick van Klink, vanklink@gmail.com

TRANSCATHETER AORTIC VALVE IMPLANTATION: CURRENT RESULTS, INSIGHTS & FUTURE CHALLENGES

Transcatheter aortaklep implantatie: huidige resultaten, inzichten & toekomst uitdagingen

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
Prof.dr. H.G. Schmidt
en volgens besluit van het College voor Promoties

De openbare verdediging zal plaatsvinden op
dinsdag 11 juni 2013 om 11.30 uur

door

Rutger-Jan Marius Nuis

geboren te Baarn

ERASMUS UNIVERSITEIT ROTTERDAM

Promotiecommissie

Promotoren:	Prof.dr. P.P.T. de Jaegere
	Prof.dr. F. Zijlstra
Overige leden:	Prof.dr. H. Boersma
	Prof.dr. A.P. Kappetein
	Prof.dr. A. Bogers
	Prof.dr. H. Suryapranata
Co-promotor:	Dr. R.T. van Domburg

Financial support for the publication of this thesis was generously provided by:

Erasmus University Rotterdam

Cardialysis BV

Merck Sharp & Dohme BV

Biotronik Nederland BV

St. Jude Medical Nederland BV

Boehringer Ingelheim BV

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

Contents

CHAPTER 1

Introduction

INTRODUCTION

In western countries, aortic stenosis is - together with mitral regurgitation - a common valvular heart problem of which its prevalence increases with age[1]. The latter is explained by the pathogenesis or aetiology of aortic stenosis. At variance with the past, valvular aortic stenosis is the result of a degenerative process that is similar to arterial atherosclerosis in most if not all patients that are currently seen in our practice. It concerns a process that is characterized by infiltration of small particles thereby inducing inflammation and ultimately calcification of the vascular structure. It is, therefore, not surprising that due to the ageing of our society, the absolute number of patients with aortic stenosis will increase[2].

Prognosis in patients with severe aortic stenosis (i.e. survival and quality of life) is dismal, in particular in case of symptoms or impaired left ventricular function irrespective of symptoms[3-5]. Yet, advanced age and the prevalence of associated cardio-vascular and non-cardiovascular antecedents and co-morbidities often render these patients less amenable to surgical aortic valve replacement (AVR) because of either high operative risk and/or long postoperative recovery. It is estimated that approximately 30 to 50% of patients with aortic stenosis are not referred for further evaluation or treatment because of the perceived risk of AVR[6, 7].

In the quest of development of less invasive procedures, transcatheter aortic valve implantation (TAVI) emerged as a novel treatment modality to treat patients who are considered too high a risk for AVR[8]. TAVI consists of a catheter-based beating heart procedure during which a trileaflet bioprosthesis is implanted into the base of the aortic root without the need of sternotomy, cardio-pulmonary bypass and cardiac arrest.

Randomised comparisons have shown TAVI to be an evidence-based alternative for AVR in patients with increased risk for AVR[9-12]. Fuelled by these results and expectations, the number of TAVI procedures has increased exponentially across the globe with speculations of its extension to lower risk patient groups[13]. Studies assessing the role of TAVI relative to AVR in patients with intermediate risk are currently performed.

Similar to every other surgical or interventional procedure, TAVI is also associated with a number adverse events such as death, stroke, bleeding- and vascular complications, rhythm and conduction abnormalities in addition to paravalvar aortic regurgitation and acute kidney injury. Obviously, outcome depends on a number of factors including patient-, procedure-, and device related factors. Insight into these factors is important to improve the results of TAVI in patients who currently undergo this procedure and before implementing TAVI in lower risk patients. This is subject of the present thesis in which the frequency but also potential pathophysiological mechanisms of perioperative complications are reported and studied.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;368:1005-1011.
2. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. *J Am Coll Cardiol.* 2012;60:1854-1863.
3. Authors/Task Force M, Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Lung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M, Guidelines ESCCfP, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document R, Popescu BA, Von Segesser L, Badano LP, Bunc M, Claeys MJ, Drinkovic N, Filippatos G, Habib G, Kappetein AP, Kassab R, Lip GY, Moat N, Nickenig G, Otto CM, Pepper J, Piazza N, Pieper PG, Rosenhek R, Shuka N, Schwammenthal E, Schwitter J, Mas PT, Trindade PT, Walther T, Joint Task Force on the Management of Valvular Heart Disease of the European Society of C, European Association for Cardio-Thoracic S. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg.* 2012;42:S1-44.
4. Ross J, Jr., Braunwald E. Aortic stenosis. *Circulation.* 1968;38:61-67.
5. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J.* 1987;8:471-483.
6. Bouma BJ, van Den Brink RB, van Der Meulen JH, Verheul HA, Cheriex EC, Hamer HP, Dekker E, Lie KI, Tijssen JG. To operate or not on elderly patients with aortic stenosis: the decision and its consequences. *Heart.* 1999;82:143-148.
7. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Barwolf C, Boersma E, Ravaud P, Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J.* 2005;26:2714-2720.
8. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation.* 2002;106:3006-3008.
9. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-1607.
10. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson

WN, Wang D, Pocock SJ, Investigators PT. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-2198.

11. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB, Investigators PT. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med.* 2012;366:1686-1695.

12. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB, Investigators PT. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med.* 2012;366:1696-1704.

13. Lange R, Bleiziffer S, Mazzitelli D, Elhmidi Y, Opitz A, Krane M, Deutsch MA, Ruge H, Brockmann G, Voss B, Schreiber C, Tassani P, Piazza N. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol.* 2012;59:280-287.

AIM AND OUTLINE OF THE THESIS

The outline of the thesis is as follows. In Part I (Chapters 2, 3 and 4), the clinical decision making and factors influencing the outcome of patients referred for TAVI are presented and discussed. Chapter 2 addresses treatment decision, in-hospital outcome and determinants of survival while Chapter 3 provides an overview of common perioperative complications. In Chapter 4, the effects of operator experience and improvements in technique and technology on outcome after TAVI are evaluated.

Part II (Chapters 5, 6 and 7) focuses on the frequency and pathophysiology of new conduction abnormalities during and after TAVI. The timing and potential mechanisms of new intraventricular conduction abnormalities during various predefined phases of TAVI are reported in Chapter 5. The persistency of these new conduction abnormalities between hospital discharge until 6 months after TAVI is evaluated in Chapter 6. The effects of new conduction abnormalities on left ventricular systolic function are discussed in Chapter 7.

Part III (Chapters 8 and 9) deals with the occurrence of peri-operative stroke, which is considered one of the most if not the most dreadful complication after any surgical or interventional procedure including TAVI because of its effects on survival and, even more important, quality of life. In Chapter 8, the frequency, timing of occurrence and cause of stroke is determined using – among others – computed tomography to assess the type of stroke and its potential mechanisms. Chapter 9 concerns similar work but in a large cohort of patients (>1000) treated in various centers and in which distinction is made between the potential causes of stroke in the acute, sub-acute and late phases following TAVI.

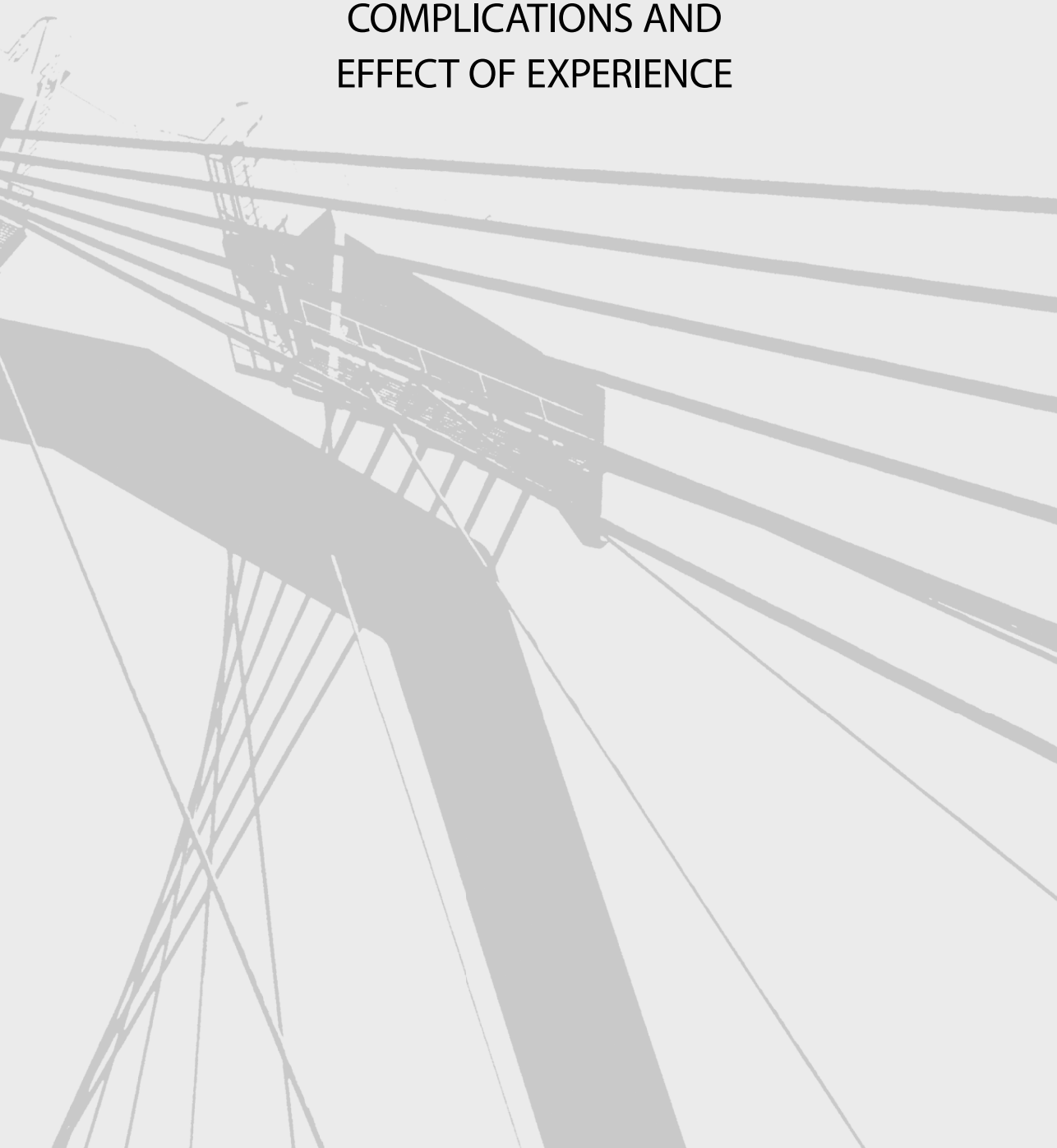
Part IV (Chapters 10 and 11) provides information on acute kidney injury (AKI). AKI concerns a clinically silent but potential harmful complication that develops during the first days after TAVI. In Chapter 10, the frequency, pathophsyiology and prognostic effect of AKI are discussed followed by an in-depth analysis of the relation between peri-operative blood transfusion and the risk of AKI in Chapter 11.

Part V (Chapter 12) discusses the prevalence of pre-operative anemia in addition to the effects of the various levels of pre-operative hemoglobin on short- and long-term mortality in patients undergoing TAVI using a 10-center study approach encompassing close to 1600 patients. The objective of this study stems from the fact that anemia is frequently seen in elderly patients while – at the same time - anemia is known to be an independent risk factor of mortality, in particular in cardiac patients.

Chapter 13 concerns a study assessing the clinical results of TAVI in a population of different origin (Latin America) where TAVI was introduced in 2008.

PART 1

CLINICAL DECISION-MAKING, COMPLICATIONS AND EFFECT OF EXPERIENCE



CHAPTER 2

Treatment decision, in-hospital outcome and determinants of survival

Patients with aortic stenosis referred for TAVI: treatment decision, in-hospital outcome and determinants of survival

R. J. Nuis · A. E. Dager · R. M. van der Boon · M. C. Jaimes · B. Caicedo · J. Fonseca · N. M. Van Mieghem · L. M. Benitez · J. P. Umana · W. W. O'Neill · E. de Marchena · P. P. de Jaegere

Published online: 14 December 2011

Abstract
Aims To assess treatment decision and outcome in patients referred for transcatheter aortic valve implantation (TAVI) in addition to predictive factors of mortality after TAVI.
Methods Three-centre prospective observational study including 358 patients. Endpoints were defined according to the Valve Academic Research Consortium.
Results Of the 358 patients referred for TAVI, TAVI was performed in 235 patients (65%), surgical aortic valve replacement (AVR) in 24 (7%) and medical therapy (MT) in 99 (28%). Reasons to decline TAVI in favour of AVR/MT were patient preference (29%), peripheral vascular disease (15%) and non-severe aortic stenosis (11%). The logistic EuroSCORE was significantly higher in patients who underwent TAVI and MT in comparison with those undergoing AVR (19 vs. 10%, $p=0.007$). At 30 days, all-cause mortality and the combined safety endpoint were 9 and 24% after TAVI and 8 and 25% after AVR, respectively. All-cause mortality was significantly lower in the TAVI group compared with the MT group at 6 months, 1 year and 2 years (12% vs. 22%, 21% vs. 33% and 31% vs. 55%, respectively, $p<0.001$). Multivariable analysis revealed that blood transfusion (HR: 1.19; 95% CI: 1.05–1.33), pre-existing renal failure (HR: 1.18; 95% CI: 1.06–1.33) and STS score (HR: 1.06; 95% CI: 1.02–1.10) were independent predictors of mortality at a median of 10 (IQR: 3–23) months after TAVI.
Conclusions Approximately two-thirds of the patients referred for TAVI receive this treatment with gratifying short- and long-term survival. Another 7% underwent AVR. Prognosis is poor in patients who do not receive valve replacement therapy.

Keywords Aortic stenosis · Transcatheter aortic valve implantation · Surgical aortic valve replacement · Treatment decision · Complications · Prognosis

The questions can be answered after the article has been published in print. You have to log in to: www.cvoi.nl.

R. J. Nuis · R. M. van der Boon · N. M. Van Mieghem · P. P. de Jaegere
Department of Cardiology, Thoraxcentre, Erasmus University, Rotterdam, the Netherlands

A. E. Dager · B. Caicedo · J. Fonseca · L. M. Benitez
Department of Cardiology, Angiografia de Occidente SA, Cali, Colombia

M. C. Jaimes · J. P. Umana
Department of Cardio-Thoracic Surgery, Fundacion Clinica Cardio Infantil, Bogota, Colombia

W. W. O'Neill · E. de Marchena
Division of Cardiology, Miller School of Medicine, University of Miami, Miami, FL, USA

J. P. Umana
Universidad del Rosario (Medical and Health Sciences School), Bogota, Colombia

P. P. de Jaegere (✉)
Thoraxcentre, 's-Gravendijkwal, 230 3015 CE Rotterdam, the Netherlands
e-mail: p.dejaegere@erasmusmc.nl

Introduction

Transcatheter aortic valve implantation (TAVI) is a catheter-based treatment for patients with aortic stenosis (AS) who are considered poor candidates for surgical aortic valve replacement (AVR). Although it is increasingly being considered the standard of care in such patients [1], not

all patients receive TAVI but instead continue medical therapy (MT). This may bear important consequences in terms of prognosis and quality of life.

Historically, the treatment decision heavily depended upon the assessment of risk of valve replacement by using the Logistic EuroSCORE (LES) or Society of Thoracic Surgeons (STS) score [2, 3]. These scores were developed to assess the operative risk of patients undergoing open-heart surgery but not for the subset of patients who are referred for TAVI. Therefore, careful patient-to-patient case evaluation by Heart Team meetings are strongly encouraged and play a crucial role in the design of randomised clinical trials [1, 4–7]. In this study, we sought to explore the reasons for the treatment decision, the treatment-specific complications and survival in patients referred for TAVI in addition to the predictive factors of mortality in those undergoing TAVI.

Methods

Patients and eligibility

The population consists of all 358 patients who were referred for TAVI at the Department of Cardiology of the Erasmus Medical Centre, Rotterdam, the Netherlands and the Departments of Cardiology and Cardio-Thoracic Surgery of Angiografia de Occidente S.A., Cali, Colombia and Fundacion Clinica Cardio Infantil, Bogota, Colombia between November 2005 and January 2011. In the three institutions, a similar database and structure of data collection and follow-up was set up at the initiation of TAVI as previously described [8].

Treatment decision (TAVI, AVR, MT) was taken by consensus during the Heart Team meeting. Details of eligibility for Medtronic Corevalve System (MCS) implantation, the bioprosthesis and technique of implantation have previously been described [8–10]. All patients underwent transfemoral (n=228) or trans-subclavian TAVI (n=7) with the 18 Fr third-generation MCS except for the first five patients treated in 2005 and 2006, in whom a 21 Fr second-generation MCS was implanted.

AVR was performed through mid-sternotomy using standard surgical techniques. In all patients a biological prosthesis was used.

Patients not undergoing valve intervention continued MT. Balloon aortic valvuloplasty (BAV) was performed in patients with AS and worsening symptoms as a bridge to TAVI or as a palliative approach in patients who could not undergo TAVI/AVR.

Data collection

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 author at each participating centre (within a Master of Science Programme of the Netherlands Institute for Health Sciences, Erasmus University Rotterdam, supported by the Erasmus-Columbus Latin-European Exchange Grant - www.erasmus-columbus.eu).

All endpoints were selected and defined according to the Valve Academic Research Consortium (VARC) [11].

Cerebrovascular events were evaluated and adjudicated by a vascular neurologist. A full blood and chemistry sample was taken before and up to 3 days after the procedure to assess the occurrence and severity of peri-procedural vascular, bleeding and kidney complications. Data on red blood cell (RBC) transfusions were recorded by the institution's blood bank. The occurrence and timing of new atrial fibrillation and postprocedural 3rd degree atrioventricular block was assessed by continuous telemetry recording.

The VARC combined safety endpoint at 30 days consisted of all-cause death, major stroke, major vascular complication, life-threatening bleeding, acute kidney injury (AKI) stage III and any in-hospital re-intervention due to prosthesis dysfunction (interventional/surgical).

Follow-up

Follow-up information of patients treated at the Erasmus Medical Centre (TAVI, AVR, MT) 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 patients treated in Colombia was obtained by the regular office visit and/or telephone contact (dedicated local research nurse 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 except for 3 patients.

Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared with the Chi-square test or Fisher's exact test. Normal and skewed continuous variables are presented as means ± SD and medians (IQR), respectively. To compare the three treatment groups, analysis of variance was used for continuous variables and

the Chi-square test for categorical variables. Kaplan-Meier survival methods were used to calculate the cumulative survival at different time intervals and the log-rank test was used to assess differences in survival. A stepwise Cox regression analysis including all variables with $p<0.10$ in the univariable analysis was used to determine independent predictors of late mortality in patients undergoing TAVI. A two-sided $p<0.05$ was considered to indicate significance and all analyses were performed with SPSS software (version 17.0).

Results

Of the 421 patients, 60 (14%) died on the waiting list at a median (IQR) of 48 (14–110) days after first medical contact and 3 (1%) were lost to follow-up. Therefore, the total study population consists of 358 patients of whom 235 (65%) underwent TAVI at a median (IQR) interval of 71 (30–119) days and 24 (7%) AVR at an interval of 63 (33–122) days. The remaining 99 patients (28%) continued MT. The reasons why AVR or MT was chosen instead of TAVI are depicted in Fig. 1. The main reason to reject TAVI in favour of AVR or MT were patient preference (29%), peripheral vascular disease (PVD, 13%) and non-severe AS (11%). The baseline characteristics of the three treatment groups are summarised in Table 1. Not unexpectedly, patients who underwent TAVI or continued MT had a significantly higher LES.

Thirty-day clinical outcome

Thirty-day all-cause and cardiovascular mortality was 9 and 6% in the TAVI group and 8 and 8% in the AVR group, respectively (Table 2). In the TAVI group, six patients died during the procedure. The cause of death was hypotension during induction of anaesthesia ($n=1$), electromechanical dissociation ($n=2$), coronary obstruction ($n=1$), left ventricular outflow tract rupture ($n=1$) and retroperitoneal haemorrhage ($n=1$). Another 14 patients died at a median of 7 (IQR: 3–13) days after TAVI due to stroke ($n=3$), heart failure ($n=2$), sudden death ($n=2$: unrecognised alternating left and right bundle branch block leading to asystole at day 8 and sudden death 1 day after discharge on day 29), sepsis ($n=2$), pneumonia ($n=2$), retroperitoneal haemorrhage ($n=2$) and cardiac tamponade ($n=1$). In the surgical group, the cause of death was ventricular fibrillation ($n=1$) and severe paravalvular aortic regurgitation ($n=1$).

Cardiac re-intervention after the index procedure was required in 3 patients in the TAVI group: immediate conversion to AVR ($n=1$), closure of a paravalvar leak 14 days after TAVI ($n=1$) and post-implantation dilatation of the MCS 21 days after TAVI ($n=1$). In the AVR group, two patients underwent re-thoracotomy for severe aortic regurgitation ($n=1$) and cardiac tamponade ($n=1$) 1 day after AVR.

Although the total rate of vascular and bleeding complications was higher in the TAVI group in comparison with the AVR group, the combined 30-day safety endpoint did not differ between the two groups (24 vs. 25%, $p=1.0$).

Follow-up

The median follow-up was 298 (IQR: 107–688) days in the TAVI group, 836 (IQR: 327–1269) days in the surgical group and 456 (IQR: 187–869) days in the medical group.

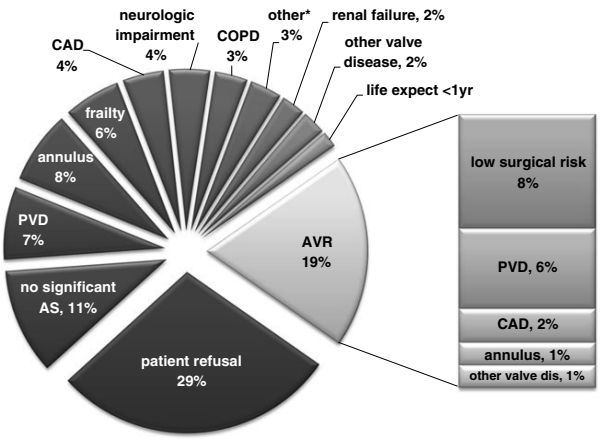


Fig. 1 Reasons to decline TAVI in favour of AVR and MT. *Four patients had another reason: severe left ventricular dysfunction (LVEF <20%); bleeding diathesis; abusive alcohol use; unknown. AS = aortic stenosis; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; PVD = peripheral vascular disease

Table 1 Baseline characteristics of patients undergoing TAVI, AVR and medical therapy

	TAVI *n*=235	AVR N=24	Medical *n*=99	p-value
Age (years), mean ± SD	80±7	78±9	80±8	0.26
Male, n (%)	116 (49)	13 (54)	42 (42)	0.32
Height (cm), mean ± SD	166±11	169±8	166±8	0.50
Weight (kg), mean ± SD	71±13	75±11	69±16	0.14
BMI, mean ± SD	26.7±4	26.4±4	24.9 5	0.34
BSA, mean ± SD	1.81±0.19	1.87±0.15	1.77±0.24	0.14
NYHA class ≥III, n (%)	177 (75)	12 (50)	53 (53)	0.091
Previous MI, n (%)	45 (19)	5 (21)	16 (16)	0.78
Previous CABG, n (%)	54 (23)	0	21 (21)	0.032
Previous PCI, n (%)	60 (26)	5 (21)	26 (26)	0.92
PVD, n (%)	30 (13)	6 (25)	28 (28)	0.002
Diabetes mellitus, n (%)	57 (24)	5 (21)	28 (28)	0.64
Hypertension, n (%)	132 (56)	12 (50)	34 (34)	0.029
Creatinine, mean ± SD	123±131	104±56	129±68	0.75
Chronic haemodialysis, n (%)	11 (5)	1 (5)	0	0.20
COPD, n (%)	78 (33)	5 (21)	31 (31)	0.59
Permanent pacemaker, n (%)	26 (11)	3 (13)	10 (10)	0.96
Atrial fibrillation, n (%)	49 (21)	8 (33)	25 (25)	0.23
Aortic valve area (cm2), mean ± SD	0.67±0.21	0.81±0.39	0.77±0.27	0.001
LV, n (%)				
- Poor (EF <30%)	34 (14)	2 (8)	10 (10)	0.89
- Moderate (EF 30–59%)	82 (35)	6 (25)	24 (24)	0.66
Mitral regurgitation grade ≥III, n (%)	28 (12)	2 (8)	5 (5)	0.29
Aortic regurgitation grade ≥III, n (%)	45 (19)	0	3 (3)	0.001
Logistic Euroscore, mean ± SD	19.1±13.7	10.1±4.3	18.9±12.1	0.007
STS score, mean ± SD	6.1±5.5	4.1±2.4	5.8±3.8	0.17

BMI body mass index, *BSA* body surface area, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *EF* ejection fraction, *NYHA* New York Heart Association, *LV* left ventricular, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PVD* peripheral vascular disease, *STS* Society of Thoracic Surgeons

Kaplan-Meier estimates of survival are shown in Fig. 2. Estimated survival at 2 years was 80% in the AVR group, 69% in the TAVI group and 45% in patients who continued MT ($p<0.001$). The median time between treatment (AVR or TAVI) or first medical contact (MT) and death was 96 (IQR: 11–679) days in the surgical group, 171 (IQR: 24–365) days in the TAVI group and 300 (IQR: 98–578) days in the MT group.

Details of adverse events beyond 30 days are summarised in Table 3. By univariable analysis, PVD, baseline creatinine, STS score, RBC transfusion and AKI were identified as potential determinants of mortality after TAVI. Multivariable analysis retained RBC transfusion (HR: 1.19; 95% CI: 1.05–1.33), pre-existing renal failure (HR: 1.18; 95% CI: 1.06–1.33) and STS score (HR: 1.06; 95% CI: 1.02–1.10) as independent predictors of mortality after TAVI

Discussion

We found that the majority of patients referred for TAVI (72%) undergo valve implantation/replacement (TAVI 65%, AVR 7%) but that nearly 30% continue MT mainly because of comorbidity and patient preference not to receive TAVI/AVR. Patients who underwent TAVI had a higher LES than those who underwent AVR, were more symptomatic with a higher prevalence of antecedent CABG and impaired renal function but less PVD. The most frequent complications after TAVI consisted of bleeding and vascular complications.

With respect to treatment allocation, the present findings most likely reflect the current 'real world' practice. The two-thirds acceptance and one-third rejection rate contrasts with randomised studies such as the Placement of AoRTic TraNscathetER valve (PARTNER) Cohort-B trial in which only 12% of the referred patients were accepted for

Table 2 Thirty-day clinical outcome in patients undergoing TAVI and AVR

	TAVI n=235	AVR n=24	p-value
Mortality, n (%)			
- All-cause	20 (9)	2 (8)	1.0
- Cardiovascular cause	13 (6)	2 (8)	0.64
Myocardial infarction, n (%)			
- All	3 (1)	1 (4)	0.32
- Periprocedural (<72 h)	2 (1)	0	1.0
Cerebrovascular complication, n (%)			
- All[1]	20 (9)	2 (8)	1.0
- Major stroke	11 (5)	1 (4)	1.0
Vascular complication, n (%)			
- All	42 (18)	0	0.036
- Major	24 (10)	0	0.14
Bleeding complication, n (%)			
- All	67 (29)	2 (8)	0.049
- Life-threatening or disabling	21 (9)	2 (8)	1.0
Acute kidney injury, n (%)			
- All	40 (17)	8 (33)	0.058
- Stage III	5 (2)	2 (8)	0.13
Cardiac re-intervention, n (%)			
- AVR	1 (1)	0	1.0
- BAV	1 (1)	0	1.0
- Other[2]	1 (1)	2 (8)	0.023
New pacemaker implantation			
- All	48 (21)	1 (4)	0.056
- For 3rd degree AV block	40 (17)	0	0.032
New atrial fibrillation	9 (5)	2 (11)	0.60
Repeat hospitalisation, n (%)[3]	3 (1)	0	1.0
Combined 30-day safety endpoint, n (%)[4]	55 (24)	6 (25)	1.0

AV atrioventricular, *AVR* aortic valve replacement, *BAV* balloon aortic valvuloplasty

Mutually non-exclusive analysis (≥1 event/patient possible)

[1]Including TIA

[2]Closure of severe paravalvar aortic regurgitation with Amplatzer closure device (n=1) in TAVI group and resternotomy for severe aortic regurgitation (n=1) and bleeding (n=1) in AVR group

[3]For symptoms of valve-related dysfunction or cardiac decompensation

[4]Composite all-cause mortality, major stroke, major vascular complication, life-threatening bleeding, acute kidney injury - stage 3, peri-procedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional)

randomised treatment allocation. Of note, we observed a significant increase in acceptance for TAVI from 2006 until 2010; it was 20% in 2006, 33% in 2007, 50% in 2008, 57% in 2009 and 81% in 2010. This is not explained by accepting less sick patients since the LES did not change over time but is most likely explained by increased experience and familiarity with the procedure in combination with an increased public awareness resulting in less patients who refuse therapy. This may also explain that – over time - less patients were redirected to surgery (29% of the surgical patients were treated in 2006; 29% in 2007; 25% in 2008; 13% in 2009 and 4% in 2010).

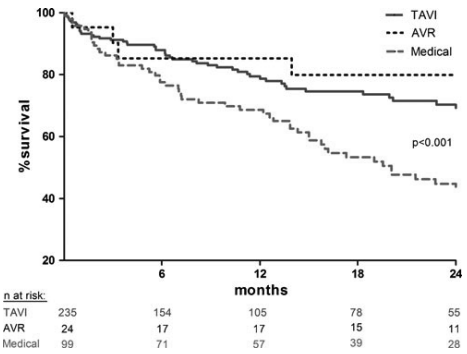


Fig. 2 Kaplan-Meier survival curve for patients undergoing TAVI, AVR and MT

Initially the LES was a critical factor in patient acceptance but a present consensus on treatment allocation by the Heart Team has become the dominant factor. This is not surprising since this score was neither designed nor validated for TAVI and does not capture the spectrum of clinical details allowing a balanced treatment decision [12, 13]. Also the LES is out of synchrony with the STS score [12, 14]. The shortcomings of the risk score models and the value of multidisciplinary patient discussion are illustrated by the web-based conference call system used in the United States to review and

Table 3 Adverse events beyond 30 days after TAVI, AVR and medical treatment

	TAVI[a]		AVR[a]		Medical[a]
	All (n=106)	Fatal (n=40)	All (n=10)	Fatal (n=5)	Fatal (n=59)
Cardiac	46 (43)	19 (48)	5 (50)	1 (20)	31 (53)
Heart failure	13 (12)	4 (10)	4 (40)	1 (20)	19 (32)
Sudden death	8 (8)	8 (20)	0	0	9 (15)
Myocardial infarction	2 (2)	2 (5)	1 (20)	0	1 (2)
Cardiac re-intervention	3 (3)[1]	0	0	0	0
Stroke or TIA	11 (10)[2]	4 (10)	0	0	2 (3)
Pacemaker implantation	9 (9)	1 (3)[3]	0	0	0
Non-cardiac	56 (53)	21 (52)	5 (50)	4 (80)	9 (15)
Infection	17 (16)	8 (20)	1 (10)	1 (20)	5 (8)
Renal failure	7 (7)	4 (10)	2 (20)	2 (40)	0
Vascular	3 (3)	0	0	0	0
Bleeding (non-cranial)	3 (3)	1 (3)	1 (10)	0	0
Neoplasm	9 (8)	4 (10)	0	0	1 (2)
Metabolic disease	2 (2)	2 (5)	0	0	0
Other	15 (14)	2 (5)[4]	1 (10)	1 (20)[5]	3 (5)[6]
Unknown	4 (4)	0	0	0	19 (32)

[a] Median follow-up was 298 (IQR: 107–688) days in the TAVI group, 836 (IQR: 327–1269) days in the AVR group and 456 (IQR: 187–869) days in the medical group

[1] Re-interventions before discharge included AVR (n=1) and post-implantation balloon aortic valvuloplasty (n=2)

[2] Including TIA (n=4); of the 11 events, 9 were ischaemic of which 2 fatal and 2 were haemorrhagic, both of which fatal

[3] Pneumothorax following pacemaker implantation (n=1)

[4] Blood transfusion reaction (n=1), euthanasia (n=1)

[5] Delirium (n=1)

[6] Obstructive pulmonary disease (n=2), lung emboli (n=1)

approve patients for TAVI, which is subsequently used in the PARTNER trial [1]. Moreover, randomisation to TAVI or AVR in the SURgery and Transcatheter Aortic Valve Implantation (SURTAVI) trial will be based upon clinical judgement by the Heart Team but not a risk score. The latter will only be used as criterion for entry into the Heart Team discussion [6].

The outcome in the TAVI group in the present study is consistent with the findings of the multi-centre observational registries [14–18]. The worst complications are death and stroke. Conceptually safety will increase when less sick patients receive TAVI. It remains to be elucidated whether stroke can be reduced by the use of embolic protection devices during the procedure. As mentioned, the most frequent complications are bleeding and vascular complications. Patient-related factors may play a role but are not the only ones. At present there is no fully proven percutaneous closure technique. Since bleeding and vascular complications are inherently associated with a series of ensuing events (e.g. transfusion) and complications (e.g. anaemia, renal dysfunction) which in turn affect short- and long-term outcome, surgical access and closure of the arterial entry site should be considered [19–23]. The need for pacemaker insertion is predominantly a device-related phenomenon. A consistently higher frequency of new pacemaker implantation after MCS implantation (up to 49%) than after Edwards implantation (up to 27%) is reported [24, 25]. This is not without clinical importance since abnormal conduction may impair left ventricular ejection fraction recovery after TAVI [26].

Follow-up was characterised by a high incidence of cardiac and non-cardiovascular events. As for immediate outcome, it is conceivable that long-term outcome will be better in less sick patients. This is the subject of investigation in an ongoing Danish study in which age ≥70 is the main selection criterion for random allocation to TAVI or AVR. (ClinicalTrials.gov, Identifier: NCT01057173).

In the present study, outcome was poor in patients who continued MT. MT was continued mainly because of Heart Team rejection for TAVI because of comorbidity. Yet, a substantial number of patients refused valve implantation/replacement. Patient preference intrinsically is bi-directional and will play an increasing role in treatment decisions due to increased public awareness. This puts the medical community

under pressure since the position statement paper on TAVI advocates not to include patient preference in the treatment decision [4]. It also raises an ethical issue since one may question whether one has the right to refuse a treatment modality if a patient who is adequately informed about treatment options, outcomes and the presence or absence of future treatment possibilities in case of failure of the index treatment persists in his/her treatment preference.

Conclusion

Up to 65 and 7% of the patients with aortic stenosis who are referred for TAVI undergo TAVI and AVR with promising results. Patients who are rejected or refuse valve replacement have a dismal prognosis.

Acknowledgements This study was supported by the Erasmus-Columbus (ERACOL) Latin-European Exchange Grant (www.erasmus-columbus.eu). Lidsa Cruz, RN (Angiografia de Occidente), is acknowledged for her contribution on database management.

References

1. Leon M, Smith C, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597–607.
2. Nashef SA, Roques F, Michel P, et al. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16:9–13.
3. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2–isolated valve surgery. Ann Thorac Surg. 2009;88:S23–42.
4. Vahanian A, Alfieri O, Al-Attar N, et al. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2008;29:1463–70.
5. Rosengart TK, Feldman T, Borger MA, et al. Percutaneous and minimally invasive valve procedures: a scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology, Functional Genomics and Translational Biology Interdisciplinary Working Group, and Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2008;117:1750–67.
6. Serruys PW. Design of a novel randomized clinical trial comparing SAVR with TAVI in patients with severe aortic stenosis at intermediate peri-operative risk. Presented at TCT Congress September 21. Washington: 2010.
7. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med. 2009;360:961–72.
8. Nuis RJ, van Mieghem NM, van der Boon RM, et al. Effect of experience on results of transcatheter aortic valve implantation using a medtronic corevalve system. Am J Cardiol. 2011;107:1824–9.
9. Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease: the task force on the management of valvular heart disease of the European society of cardiology. Eur Heart J. 2007;28:230–68.
10. Grube E, Schuler G, Buellesfeld L, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol. 2007;50:69–76.
11. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J. 2011;32:205–17.
12. Head SJ, Kappetein AP. Transcatheter aortic valve implantation after PARTNER: what is up next? EuroIntervention. 2010;6:560–1.
13. Rosenhek R, Iung B, Tornos P, et al. ESC Working group on valvular heart disease position paper: assessing the risk of interventions in patients with valvular heart disease. Eur Heart J. 2011 epub ahead of print.
14. Piazza N, Wenaweser P, van Gameren M, et al. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons Predicted Risk of Mortality score in patients implanted with the CoreValve ReValving system–a Bern-Rotterdam Study. Am Heart J. 2010;159:323–9.
15. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J. 2011;32:198–204.
16. Rodes-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol. 2010;55:1080–90.
17. Eltchaninoff H, Prat A, Gilard M, et al. Transcatheter aortic valve mplantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J. 2011;32:191–7.
18. Lefevre T, Kappetein AP, Wolner E, et al. One year FU of the multi-centre European PARTNER transcatheter heart valve study. Eur Heart J. 2011;32:148–57.
19. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation. 2011;123:299–308.
20. Nuis RJ, Van Mieghem NM, Tzikas A, et al. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2011;77:881–9.
21. Van Mieghem NM, Nuis RJ, Tzikas A, et al. Prevalence and prognostic implications of baseline anaemia in patients undergoing transcatheter aortic valve implantation. EuroIntervention. 2011;7:184–91.
22. Ducrocq G, Francis F, Serfaty JM, et al. Vascular complications of transfemoral aortic valve implantation with the Edwards SAPIEN prosthesis: incidence and impact on outcome. EuroIntervention. 2010;5:666–72.
23. Van Mieghem NM, Nuis RJ, Piazza N, et al. Vascular complications with transcatheter aortic valve implantation using the 18 Fr

Medtronic CoreValve System(R): the Rotterdam experience. EuroIntervention. 2010;5:673–9.
24. Thielmann M, Wendt D, Eggebrecht H, et al. Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. Ann Thorac Surg. 2009;88:1468–74.
25. Roten L, Wenaweser P, Delacretaz E, et al. Incidence and predictors of atrioventricular conduction impairment after transcatheter aortic valve implantation. Am J Cardiol. 2010;106:1473–80.
26. Tzikas A, van Dalen BM, Van Mieghem NM, et al. Frequency of conduction abnormalities after transcatheter aortic valve implantation with the Medtronic-CoreValve and the effect on left ventricular ejection fraction. Am J Cardiol. 2011;107:285–9.

CHAPTER 3

In-hospital complications after transcatheter aortic valve implantation revisited according to the Valve Academic Research Consortium definitions

Original Studies

In-Hospital Complications After Transcatheter Aortic Valve Implantation Revisited According to the Valve Academic Research Consortium Definitions

Rutger-Jan Nuis,[1] MSc, Nicolo Piazza,[1] MD, Nicolas M. Van Mieghem,[1] MD, Amber M. Otten,[1] MSc, Apostolos Tzikas,[1] MD, Carl J. Schultz,[1] MD, PhD, Robert van der Boon,[1] MSc, Robert-Jan van Geuns,[1] MD, PhD, Ron T. van Domburg,[1] PhD, Peter J. Koudstaal,[2] MD, PhD, Arie Pieter Kappetein,[3] MD, PhD, Patrick W. Serruys,[1] MD, PhD, and Peter P.T. de Jaegere,[1*] MD, PhD

Objectives: To determine the occurrence of in-hospital complications after transcatheter aortic valve implantation (TAVI) according to the Valve Academic Research Consortium (VARC) criteria in addition to the length of stay (LOS). Background: The absence of uniformity in endpoint definitions challenges the comparison between previously reported major adverse cerebro- and cardiovascular event rates after TAVI. To address this, in 2009, the VARC was established aiming to provide standardized endpoint definitions for TAVI clinical trials. Methods: Between November 2005 and September 2010, we prospectively enrolled 150 consecutive patients who underwent TAVI with the Medtronic CoreValve System in our institution. Complications, prosthetic valve associated endpoints, and therapy-specific endpoints were defined according to the definitions provided by the VARC. Results: The mean age (±SD) was 81 (±7) years and 55% were female. Thirty-day or in-hospital mortality was 11%, and the 30-day combined safety endpoint was 22%. Seventy-six patients (51%) had ≥1 cardiovascular and/or noncardiovascular complication of whom 16 also underwent a new permanent pacemaker implantation (PPI). In the 74 patients with uneventful TAVI, 12 patients (8%) underwent PPI. TAVI was truly uneventful in 62 patients (41%). Bleeding complications were observed most frequently (31%), followed by acute kidney injury (18%), vascular complications (16%), and stroke/TIA (11%). The median LOS in patients with a complicated and a truly uncomplicated TAVI was 14.0 (8.0–20.5) and 8.0 (7.0–10.8) days, respectively ($P < 0.001$). Conclusion: TAVI was associated with ≥1 cardiovascular and/or noncardiovascular event in 51% of the patients; new PPI was needed in another 8%, and TAVI was truly uncomplicated in 41%. Complications and need for new PPI significantly prolonged LOS.

Key words: heart disease; complications adult cath/intervention; length of stay; aortic stenosis

[1]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
[3]Department of Cardio-Thoracic surgery, Erasmus Medical Center, Rotterdam, The Netherlands

Conflict of interest: PJ is a proctor for Medtronic and NP is a consultant to Medtronic.

*Correspondence to: Peter P.T. de Jaegere, MD, PhD, Thoraxcenter, s-Gravendijkwal 230, 3015 CE, Rotterdam, the Netherlands.
E-mail: p.dejaegere@erasmusmc.nl

Received 17 January 2011; Revision accepted 22 January 2011

DOI 10.1002/ccd.23018
Published online in Wiley Online Library (wileyonlinelibrary.com)

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a new treatment modality for patients with aortic stenosis who are considered poor surgical candidates because of age and/or severe comorbidities. Given the lesser invasive nature of TAVI in comparison with surgical aortic valve replacement (AVR), TAVI is increasingly being used to treat high-risk patients albeit in the absence of sound data of safety and efficacy [1–4]. Safety is generally defined by the occurrence of major adverse cardio- and cerebrovascular events (MACCE) during or immediately after the procedure up to 30 days and includes death, stroke, myocardial infarction, bleeding, and vascular complications. The current information on safety of TAVI stems from predominantly single-center observations with differences in data collection and, above all, definitions [5–15]. Increasing awareness among the growing heterogeneity of endpoint definitions for reporting the results of TAVI [16–18] lead to the development of an international multidisciplinary expert group (Valve Academic Research Consortium—VARC), which was established in 2009 with the specific goal of defining clinical trial endpoint definitions for TAVI [19]. In line with this consortium, we sought to determine the in-hospital events that occur during and/or immediately after TAVI in a series of 150 consecutive patients. Because it may be difficult to collect all complications that occur, we also determined the length of stay (LOS), which is a nonspecific outcome measure that can be used as a composite indicator of adverse events.

MATERIALS AND METHODS

Study Population and Procedure

In this single center study, a total of 150 consecutive patients underwent TAVI with the Medtronic CoreValve System (MCS) between November 2005 and September 2010. Eligibility for TAVI has been described in detail elsewhere as well as the prosthesis and procedure [8,10].

In brief, patients with valvular aortic stenosis (AVA < 1.0 cm^2 or ≤ 0.6 cm^2/m^2) who were considered poor surgical candidates were eligible for TAVI. The latter was initially defined by age ≥ 80 years or a logistic EuroSCORE of ≥ 20 (November 2005–October 2006) and subsequently by age ≥ 75 or a logistic EuroSCORE ≥ 15 (October 2006–present). Patients ≥ 65 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. Patients were not eligible in case of a recent vascular event (stroke, myocardial infarction, and percutaneous intervention), a planned intervention within 30 days, infection, GFR < 20 ml/min, life expectancy less than 1 year, hypersensitivity, or contraindication to aspirin or clopidogrel. Some patients with GFR < 20 ml/min, however, were proposed TAVI after Heart Team consensus. Following this selection process, every patient gave written informed consent for the treatment, and all clinical data were collected in the context of a structured follow-up to which every patient treated in our department is subjected in accordance with IRB approval.

In the beginning of our series, TAVI was performed under a regimen of dissociated anesthesia (sedation and analgesia but no intubation and ventilation), later on replaced by a strategy of general anesthesia for the purpose of both patient and operator comfort. The transarterial femoral approach was the default access route, and surgical cut down was only performed in patients who were treated with the second generation 21 F MCS (the initial five patients) or those treated by the subclavian approach due to severe peripheral vascular disease (four patients of which one with the 21 F device). This resulted in a total of 142 patients in whom a truly percutaneous transfemoral approach was attempted.

Premedication regimen started 3 days before the procedure and consisted of aspirin 80 mg once daily and clopidogrel 75 mg once daily or a loading dose of clopidogrel of 300 mg one day of the procedure. During the postprocedural course, a dual antiplatelet strategy of aspirin 80 mg and plavix 75 mg was prescribed, each daily, for 6 months, followed by aspirin 80 mg lifelong.

Collection of Data and Outcome Measures

All predefined patient- and procedure-related variables were entered into a dedicated database [10]. Both the logistic EuroSCORE and the STS score were calculated.

All cardiovascular and noncardiovascular complications, prosthetic valve associated endpoints, and therapy-specific endpoints were defined according to the definitions provided by the VARC [19]. Death, myocardial infarction, stroke, vascular and bleeding complications, and new-onset conduction abnormalities were collected during or immediately after TAVI. All cerebrovascular events were evaluated and adjudicated by a vascular neurologist who reassessed patients with the event daily. Serum creatinine results up to 72 hr after the procedure was collected to identify patients with acute kidney injury (AKI), and data on red blood

TABLE I. Baseline Characteristics and Medication Use in Patients Undergoing TAVI

	$n = 150$
Baseline patient characteristics	
Age, years; median (IQR)	81 ± 7
Male, *n* (%)	68 (45)
Height (cm), mean ± SD	167 ± 9
Weight (kg), mean ± SD	73 ± 13
Body mass index, mean ± SD	25.9 ± 4.0
Body surface area, mean ± SD	1.82 ± 0.20
NYHA class III or IV, *n* (%)	118 (79)
Previous cerebrovascular event, *n* (%)	34 (23)
Previous myocardial infarction, *n* (%)	39 (26)
Previous coronary artery bypass graft surgery, *n* (%)	36 (24)
Previous percutaneous coronary intervention, *n* (%)	41 (27)
Diabetes mellitus, *n* (%)	33 (22)
Hypertension, *n* (%)	70 (47)
Glomerular filtration rate < 60 ml/min, *n* (%)	84 (56)
Chronic haemodialysis, *n* (%)	8 (5)
Chronic obstructive pulmonary disease, *n* (%)	41 (27)
Permanent pacemaker, *n* (%)	13 (9)
Atrial fibrillation, *n* (%)	38 (25)
Aortic valve annulus (mm), mean ± SD	22.6 ± 2.2
Left ventricular ejection fraction £35%, *n* (%)	16 (11)
Aortic valve area (cm^2), mean ± SD	0.64 ± 0.20
Mean gradient (mm Hg), mean ± SD	46 ± 17
Mitral regurgitation grade ≥ III, *n* (%)	23 (15)
Aortic regurgitation grade ≥ III, *n* (%)	44 (29)
Logistic Euroscore, median (IQR)	12.3 (9.1–18.4)
STS score, median (IQR)	6.1 (3.7–12.5)
Baseline medication use	
Antiplatelets	104 (69)
Diuretics	88 (59)
ACE inhibitors	42 (28)
Angiotensin II antagonists	28 (19)
Betablockers	78 (52)
Calcium antagonists	34 (23)
Antiarrythmics	9 (6)
Statins	68 (45)

Abbreviations: ACE, angiotensin converting enzyme; NYHA, New York Heart Association.

cell (RBC) transfusions were recorded by our institution's blood bank laboratory.

Echo-Doppler cardiography was performed the day before TAVI and within 7 days after TAVI. Details of the methods of echocardiographical data collection and analysis have previously been described [20]. Twelve-lead electrocardiography was obtained at a median of 1 day (IQR: 1-1) before and 1 day (IQR: 1-1) after treatment and examined by an independent core laboratory (Cardialysis, Rotterdam, The Netherlands) for the occurrence of new-onset left bundle branch block. Information on additional treatment including antibiotic drugs and the implantation of a new permanent pacemaker were collected before hospital discharge.

LOS was analyzed for all patients excluding patients who died during TAVI (i.e., before leaving the catheterization room). Cardiac care unit (CCU) stay and total LOS were defined by the time period from the day of the procedure until the day of Medium Care transfer and hospital discharge, respectively. In patients who were discharged after TAVI to the referring institution, total LOS was defined by total time spent in the treating and the referring hospital. In patients who died after TAVI but before planned discharge, LOS was defined by the time period from the day of the procedure until the day of death. In addition, the location to which the patient was discharged was determined and defined as follows: 1] home, 2] nursing home, and 3] rehabilitation center.

Statistical Management

LOS was expressed both as median (IQR) and mean (±SD). Normally distributed continuous variables were expressed as mean (±SD) and analyzed using the Student's *t*-test. Skewed distributed continuous variables were expressed as medians (IQR) and analyzed by the Mann–Whitney *U* test. Categorical variables were expressed as percentages and analyzed by the Pearson chi-square test or, when indicated, by the Fisher's exact test. Kaplan–Meier survival methods were used to present a 30-day survival curve. Two-sided *P*-values < 0.05 were considered to indicate statistical significance. All statistical analyses were performed with SPSS software version 17.0 (SPSS Institute, Chicago, IL).

RESULTS

The baseline characteristics of the population are summarized in Table I. In-hospital cardiovascular and noncardiovascular complications, prosthetic valve associated endpoints, and therapy-specific endpoints are summarized in Table II. Details on in-hospital or 30-day mortality, cerebrovascular complications, bleeding and vascular complications, and pacemaker implantations are presented in Tables III–VI, respectively. All cause and cardiovascular cause in-hospital or 30-day mortality was 11% ($n = 16$) and 7% ($n = 11$), respectively. The overall combined safety endpoint at 30 days was 22% ($n = 33$, Table II), but decreased to 16% in the second half of the cohort ($P = 0.076$) and tended to be higher among patients with more extensive risk profiles (EuroSCORE ≥ 20% or STS score ≥ 10%) compared to those at lower risk (27 vs. 19%, $P = 0.28$).

Seventy-six patients (51%) had ≥1 cardiovascular and/or noncardiovascular complication. Bleeding

TABLE II. In-Hospital Cardiovascular and Noncardiovascular Complications, Prosthetic-Valve Associated, Therapy-Specific, and Echocardiographic Results Following TAVI

	n (%)
Cardiovascular and noncardiovascular complications	
Cardiovascular complications	
Mortality (30-day or in hospital)	
All cause	16 (11)[a]
Cardiovascular cause	11 (7)[a]
Myocardial infarction, *n* (%)	
Periprocedural (<72 hr)	1 (1)
Spontaneous (>72 hr)	0
Stroke, *n* (%)	
Major	10 (7)
Minor	1 (1)
TIA	5 (3)
Vascular	
Major	9 (6)
Minor	15 (10)
Bleeding	
<24 hr	
Life-threatening or disabling	11 (7)
Major	21 (14)
Minor	7 (5)
>24 hr	
Life-threatening or disabling	4 (3)
Major	3 (2)
Minor	1 (1)
Noncardiovascular complications	
Acute kidney injury[b]	
Stage I	20 (14)
Stage II	3 (2)
Stage III	3 (2)
Combined safety endpoint (at 30 days)[c]	33 (22)
Prosthetic valve-associated endpoints	
Conduction disturbances	
New left bundle branch block	69 (46)
New third-degree atrioventricular block	22 (15)
New permanent pacemaker implantation	28 (19)
Worsening mitral valve regurgitation	7 (5)
Worsening mitral valve stenosis	0
Left ventricular outflow tract rupture	1 (1)
New ventricular septal defect	1 (1)
Therapy-specific endpoints	
Valve-in-valve implantation	8 (5)[d]
Postimplantation balloon dilatation	22 (15)
Unplanned cardiopulmonary bypass use	0
In-hospital reintervention	2 (1)
Echocardiography	
Aortic valve area (cm^2), mean ± SD	1.7 ± 0.5
Mean aortic gradient (mean ± SD)	9 ± 4
Mitral regurgitation grade ≥ III [*n* (%)]	26 (17)
Aortic regurgitation grade ≥ III [*n* (%)]	20 (13)

Mutually nonexclusive analysis (≥1 event/patient possible) except for combined safety endpoint.

[a]Including three intraprocedural deaths.

[b]Eight patients with preprocedural haemodialysis and three patients who died during TAVI were excluded from the analysis of AKI.

[c]Composite all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury-stage III, myocardial infarction, and repeat procedure for valve related dysfunction.

[d]Indications: "too deep" prosthesis positioning within left ventricular outflow tract in six patients and valve embolization in two patients.

complications were the most frequent (31%), followed by AKI (18%), vascular complications (16%), and stroke or TIA (11%). In these 76 patients, 16 patients underwent permanent pacemaker implantation (PPI). Among the 74 patients without a cardiovascular and/or noncardiovascular complication, 12 patients (8%) underwent PPI. TAVI was uncomplicated and without PPI in 62 patients (41%).

Infectious complications were seen in 35 patients (23%) of which urinary tract infection was the most frequent (10%), followed by pulmonary and access site infection (5% and 3%, respectively).

In total, 14 patients died before hospital discharge (9%) of whom three died during the procedure. As a result, 147 patients (98%) were eligible for the analysis of LOS. The median and mean CCU stay in the entire cohort was 1.0 (IQR, 1.0–2.0) day and 2.0 (±2.7) days, respectively. The total LOS showed to be 10 (IQR, 7.0–17.0) days and 13.4 (±9.4) days. The LOS was significantly shorter in the 62 patients with a truly uneventful procedure in comparison with the 85 of the 147 patients (58%) who suffered a cardiovascular and/or noncardiovascular complication and/or underwent a new PPI [8.0 (7.0–10.8) vs. 14.0 (8.0–20.5) days, $P < 0.001$]. Also, the LOS of patients with an uneventful procedure showed an almost normal distribution (median 8.0, mean 9.2) and was associated with a narrow IQR of 7.0–10.8. LOS in patients with an eventful procedure was skewed (median 14.0, mean 16.4) and variable (IQR 8.0–20.5). A total of 136 patients were discharged from the hospital, of whom the majority (108 patients or 79%) was discharged home. Eleven other patients (8%) were discharged to the referring center, 14 (10%) to a nursing home, and 3 patients (2%) to a rehabilitation center.

DISCUSSION

We found that 51% of the patients who underwent TAVI suffered ≥1 cardiovascular and/or noncardiovascular complication and that another 8% of the patients underwent PPI after TAVI. TAVI was uncomplicated and without additional treatment in 41%. As expected, in-hospital LOS in patients with an uneventful procedure was significantly shorter (median: 8 days) than in patients with complicated TAVI (median: 14 days).

Cerebrovascular Complications

Overall, we found a similar frequency of the so-called major adverse cardiovascular and cerebrovascular complications in comparison with previously reported data [5–15]. By and large, the mortality after TAVI is 10% (Fig. 1), which may not be surprising

TABLE III. In-Hospital or 30-Day Mortality Following TAVI

Event number	*n* in cohort	Time of death (days)	Timing	Mortality cause	Cardiovascular cause
1	10	6	Predischarge	Cardiac tamponade	Yes
2	41	29	Predischarge	Sepsis	No
3	49	0	Intraprocedural	Induction of anaesthesia	No
4	53	24	Postdischarge	Major stroke	Yes
5	55	11	Predischarge	Sepsis	No
6	59	8	Predischarge	Asystole	Yes
7	64	9	Predischarge	Major stroke	Yes
8	70	30	Predischarge	Heart failure	Yes
9	72	29	postdischarge	Sudden death	Yes
10	87	0	Intraprocedural	Left ventricular outflow tract rupture	Yes
11	89	14	Predischarge	Paravalvular regurgitation grade IV	Yes
12	90	0	Intraprocedural	Elektromechanical dissociation	Yes
13	104	28	Predischarge	Pneumonia	No
14	121	32	Predischarge	Pneumothorax after pacemaker implantation	Yes
15	132	28	Predischarge	Pneumonia	No
16	145	3	Predischarge	Major stroke	Yes

given the nature of the patients that are currently selected to undergo TAVI and the treatment itself. At variance with previous data, however, we found a higher incidence of stroke and TIA (11%). Grube et al. [8] reported an incidence of 10% while in other studies, it varied between 3 and 6% [9,14]. This large variation is most likely attributable to differences in observation and definitions used to report outcomes, in general, and stroke in particular [21]. In this study, a vascular neurologist was consulted in case a neurologic deficit was observed during the daily rounds after TAVI, and this may explain the higher incidence of stroke/TIA in comparison with previous reports. Next to death, stroke is the most devastating periprocedural complication. Moreover, none of the patients who sustained a major stroke was discharged to home after the procedure. The aetiology and determinants of stroke need to be established so to be able to improve patient selection, and, potentially, the procedure itself. Kahlert et al. [22] and Ghanem et al. [23] sought to investigate the underlying cause and found that clinically silent foci of restricted diffusion on cerebral magnetic resonance imaging were detected in the majority of patients undergoing TAVI (84% and 73%, respectively), which may reflect the pathophysiological associations between periprocedural cerebral embolization and the occurrence of stroke. Although the latter is a plausible explanation, it should be recognized that stroke is not always caused by atherosclerotic debris. The present study identified two patients with a watershed infarction, which in itself is reported to be associated with haemodynamic changes during cardiac surgery [24,25].

TABLE IV. In-Hospital Cerebrovascular Complications Following TAVI

Event number	*n* in cohort	Time of CT (days)	Clinical symptoms lasting ≥24 hr	CT result	Rankin score ≥2 and NIHSS score ≥3[a]	Stroke classification	Discharge
1	7	1	No	Negative imaging	No	TIA	Home
2	16	3	Yes	Ischemic lesion	Yes	Major stroke	Stroke unit
3	17	2	Yes	Ischemic lesion	Yes	Major stroke	Stroke unit
4	18	7	No	Negative imaging	No	TIA	Home
5	19	1	No	Negative imaging	No	TIA	Home
6	22	6	No	Negative imaging	No	TIA	Home
7	26	6	Yes	Ischemic lesion	Yes	Major stroke	Rehabilitation center
8	44	0	Yes	Negative imaging	Yes	Major stroke	Rehabilitation center
9	53	0	Yes	Ischemic lesion	Yes	Major stroke	Death
10	54	2	Yes	Negative imaging	No	Minor stroke	Home
11	64	6	Yes	Ischemic lesion	Yes	Major stroke	Death
12	85	3	No	Negative imaging	No	TIA	Home
13	105	7	Yes	Ischemic lesion	Yes	Major stroke[b]	Nursing home
14	119	2	Yes	Ischemic lesion	Yes	Major stroke	Rehabilitation center
15	138	6	Yes	Ischemic lesion	Yes	Major stroke	Nursing home
16	145	1	Yes	Ischemic lesion	Yes	Major stroke	Death

Abbreviations: CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack.
[a]At 7 days or at discharge.[b]Followed by a second stroke 2 days later.

TABLE V. In-Hospital Bleeding and Vascular Complications Occurring <24 hr and >24 hr After the Initiation of TAVI

Event number	*n* in cohort	Source of event	Event specification	Additional intervention	HB drop (g/dl)	*n* RBC transfusions	Bleeding classification	VC classification
<24 hr after start TAVI								
1	1	Access site			2.4	5	Life threatening	Major
2	2	Access site + thoracic aorta	Thoracic aortic dissection	Balloon dilation	2.7	4	Life threatening	Major
3	7	Access site	Retroperitoneal hemorrhage		5.2	3	Life threatening	Minor
4	10	Myocardium	Cardiac tamponade	Pericardiocentesis + thoractomy	5.8	13	Life threatening	No
5	21	Access site	Retroperitoneal hemorrhage	Surgical repair	7.4	9	Life threatening	Major
6	22	Access site (radial artery)			2.6	2	Major	Minor
7	24	Access site			3.4	3	Major	Minor
8	31	Access site			3.9	0	Major	No
9	34	Access site	Femoral perforation		4.7	0	Major	No
10	36	Access site (radial artery)			2.3	2	Major	Minor
11	40	Access site	Prostar failure	Surgical exploration	4.0	0	Major	Minor
12	41	Access site	Prostar failure	Surgical exploration[a]	1.6	0	Minor	Major
13	44	Access site			2.7	2	Major	Minor
14	50	Access site			2.1	2	Major	Minor
15	51	Access site	Prostar failure	Surgical exploration	3.4	4	Life threatening	Major
16	52	Access site			2.9	1	Minor	No
17	56	Myocardium	Cardiac tamponade	Pericardiocentesis	4.2	4	Life threatening	No
18	60	Access site	Prostar failure	Surgical exploration	4.4	2	Major	Minor
19	81	Access site	Prostar failure	Stenting	0.3	2	Major	Major
20	82	Access site			3.7	0	Major	No
21	83	Access site			1.9	1	Minor	No
22	84	Access site			1.1	1	Minor	No
23	86	Access site	Prostar failure	Stenting[b], surgical repair	Unknown	7	Life threatening	Major
24	87	Myocardium	Fatal LVOT rupture		na	na	Life threatening	No
25	97	Access site			2.4	1	Minor	No
26	98	Access site (radial artery)			1.3	0	Minor	No
27	99	Access site	Prostar failure	Stenting	0.6	2	Major	Minor
28	103	Access site			2.1	1	Minor	No
29	105	Access site			2.3	2	Major	Minor
30	109	Access site	Prostar failure	Surgical exploration	0.3	3	Major	Minor
31	111	Access site	Prostar failure	Surgical repair	0.6	9	Life threatening	Major
32	112	Access site			2.9	3	Major	Minor
33	113	Access site (radial artery)			2.6	2	Major	Minor
34	117	Access site	Prostar failure	Stenting	2.9	2	Major	Minor
35	120	Access site			1.0	2	Major	No
36	121	Access site	Prostar failure	Stenting	1.9	1	No	Major
37	122	Access site			2.4	2	Major	No
38	134	Access site			3.9	0	Major	No
39	141	Pleural cavity	Hematothorax	Pleural drainage	4.2	2	Life threatening	No
40	146	Access site			1.3	2	Major	Minor
>24 hr after start TAVI								
41	24	Myocardium	Cardiac tamponade	Pericardiocentesis	2.9	5	Life threatening	No
42	26	Genitourinary	Hematuria		1.3	1	Minor	No
43	86	Gastrointestinal	Melaena		2.1	10	Life threatening	No
44	92	Gastrointestinal	Melaena		0.8	5	Life threatening	No
45	100	Genitourinary	Hematuria		1.6	2	Major	No
46	123	Gastrointestinal	Angiodysplasia	Coagulation	2.6	4	Life threatening	No
47	130	Genitourinary	Hematuria		3.7	0	Major	No

All access site bleeding sources occurred at femoral artery unless specified otherwise.

Abbreviations: HB, hemoglobin; LVOT, left ventricular outflow tract; RBC, red blood cell; VC, vascular complication.

[a]Leading to infection, sepsis, and subsequent death.

[b]Leading to leg ischemia.

TABLE VI. In-Hospital Permanent Pacemaker Requirements After TAVI

Event number	*n* in cohort	Baseline ECG	Temporary PM	Time of PPI (days)	Reason for time of PPI	Indication for PPI	Timing
<7 days after TAVI							
1	14	SR, LAFB	No	4	Postprocedural new-onset	Third degree AVB	Postprocedural
2	24	SR, LBBB	No	6	Uncertainty of indication	Third degree AVB	Intraprocedural
3	30	SR, RBBB	Yes	6	Logistical issue	Third degree AVB	Intraprocedural
4	33	SR, NC	Yes	6	Logistical issue	Third degree AVB	Intraprocedural
5	47	SR, RBBB	Yes	6	Temporary fever or infection	Third degree AVB	Intraprocedural
6	69	SR, RBBB	Yes	2	None	Third degree AVB	Intraprocedural
7	73	SR, RBBB	Yes	6	Temporary fever or infection	Third degree AVB	Intraprocedural
8	75	SR, NC	Yes	1	None	Third-degree AVB	Intraprocedural
9	97	SR, AV1B, LBBB	Yes	6	Logistical issue	Third-degree AVB	Intraprocedural
10	103	AF,RBBB	Yes	4	Logistical issue	Third-degree AVB	Intraprocedural
11	106	SR	Yes	6	Postprocedural new-onset	slow ventricular response with AF	Postprocedural
12	136	SR, LBBB	Yes	6	Postprocedural new-onset	Third-degree AVB	Postprocedural
7–30 days after TAVI							
13	8	SR, NC	No	18	Postprocedural new-onset	Second-degree AVB	Postprocedural
14	54	AF, NC	Yes	7	Logistical issue	Third-degree AVB	Postprocedural
15	66	AF, NC	Yes	9	Uncertainty of indication	Third-degree AVB	Intraprocedural
16	71	SR, NC	Yes	7	Logistical issue	Third-degree AVB	Intraprocedural
17	81	AF, LBBB	Yes	14	Temporary fever or infection	Third-degree AVB	Intraprocedural
18	91	SR, NC	Yes	18	Temporary fever or infection	Third-degree AVB	Intraprocedural
19	92	AF, LAFB	Yes	8	Uncertainty of indication	slow ventricular response with AF	Intraprocedural
20	95	ST	Yes	26	Postprocedural new-onset	Third-degree AVB	Postprocedural
21	117	AF	Yes	20	Postprocedural new-onset	Third-degree AVB	Postprocedural
22	121	SR, incomplete LBBB	Yes	12	Neurocognitive dysfunction	Third-degree AVB	Postprocedural[a]
23	123	SR, LBBB	Yes	12	Logistical issue	Third-degree AVB	Postprocedural
24	131	AF	Yes	10	Postprocedural new-onset	slow ventricular response with AF	Postprocedural
25	141	SR, NC	Yes	14	Uncertainty of indication	Third-degree AVB	Intraprocedural
26	146	SR, NC	Yes	11	Logistical issue	Third-degree AVB	Intraprocedural
>30 days after TAVI and before discharge							
27	9	SR, NC	No	46	Postprocedural new-onset	NSVT	Postprocedural
28	105	SR, NC	No	41	Postprocedural new-onset	Brady–tachy syndrome	Postprocedural

Abbreviations: AF, atrial fibrillation; AV1B, 1st degree atrioventricular block; ECG, electrocardiogram; incl, incomplete; LAFB, left anterior fascicular block; LBBB, left bundle branch block; NC, normal conduction; NSVT, nonsustained ventricular tachycardia; PPI, permanent pacemaker implantation; RBBB, right bundle branch block; SR, sinus rhythm.

[a]PPI leading to pneumothorax and subsequent death at day 32.

Therefore, it remains to be seen to what extent filters, which are positioned in the aortic arch and which are capable of capturing small atherosclerotic emboli, will reduce the incidence of stroke after TAVI. Proper homeostasis may be equally important and highlights the fact that TAVI is a multidisciplinary treatment including a cardiovascular anesthesiologist [4].

Vascular and Bleeding Complications

Depending on the definition used, vascular complications during TAVI may occur in up to 34% of patients and are associated with a two- or threefold higher 30-day mortality [18,26–28]. The present study showed a 6% and 10% occurrence of major and minor vascular complications, respectively. Essential elements that

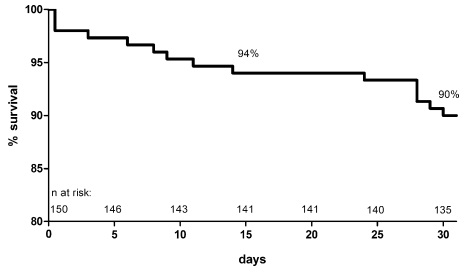


Fig. 1. Kaplan–Meier survival up to 30 days after TAVI.

should be addressed to minimize the occurrence and potential deleterious consequences of vascular complications include careful patient selection with standard diagnostic catheterization and multislice computed tomography to assess access site vessel diameter, severe tortuosity, and circumferential calcification. In addition, the use of fluoroscopy or echo-Doppler techniques during femoral puncturing when using a Seldinger technique may help to avoid femoral perforations, whereas a control angiogram at the end of the procedure may detect unsuccessful hemostasis when a percutaneous technique is used for vascular closure. Given the frequency and the clinical and economic effects of these complications, one may consider the use of a limited surgical vascular access and closure that consists of the exposure of the common femoral artery without its dissection free of its surrounding supporting structures.

With the exception of one event, all observed vascular complications in the present study were found to be associated with overt bleeding events. In total, there were 11 life-threatening or disabling, 21 major, and 7 minor overt bleeding events during or within 24 hr; another eight bleeding events (four life-threatening, three major, and one minor) were diagnosed beyond 24 hr after TAVI. An important marker that distinguishes between the degree of severity of bleeding and vascular complications proposed by the VARC is the associated number of required RBC transfusions. Irrespective of indication, our study reveals that ~70% of all patients underwent ≥1 RBC transfusion during the index-hospitalization period of whom only 33% were associated with an overt bleeding event (Fig. 2).

Acute Kidney Injury

The observed frequency of acute kidney injury (AKI) of 18% with the need of initiation of hemodialysis in 2% is in line with previous studies reporting a frequency that ranges from 12 to 28% [29,30]. Both studies found periprocedural RBC transfusion to be an important predictor of AKI, which in itself—according to the results of Bagur et al.—was independently associated with 30-day mortality. The pathophysiological interaction between periprocedural RBC transfusions and AKI following TAVI remains uncertain. Nevertheless, patients with any of these risk factors require close monitoring during the early postprocedural days and potentially thereafter.

Permanent Pacemaker Implantation

In 28 patients, a new permanent pacemaker was implanted after TAVI. The reported frequency of new

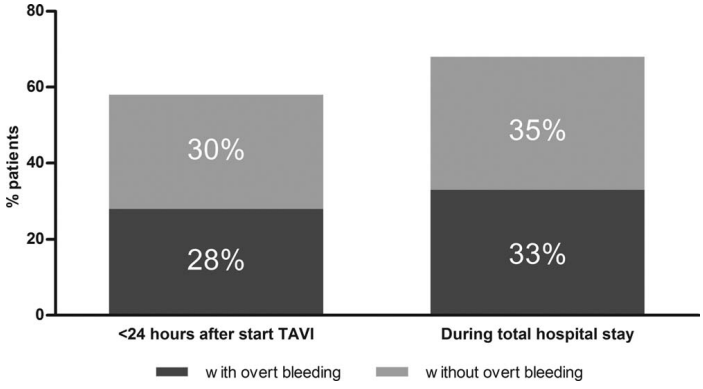


Fig. 2. Percentage of patients who underwent at least 1 RBC transfusion with or without associated overt bleeding. Abbreviations: RBC, red blood cell.

PPI after TAVI varies between 4 and 47% [12,31]. This wide variation is not surprising given the differences in threshold for PPI between physicians and institutions. TAVI is a relatively new and still experimental treatment applied in elderly patients with or without severe comorbidity and/or antecedent disease. The current guidelines of pacemaker implantation may not suffice in this population and specific treatment. As for stroke, the clarification of the etiology of atrioventricular conduction abnormalities during TAVI may help. Clinical observations in small series of patients who underwent TAVI indicate that both patient (e.g., thickness of interventricular septum and noncoronary cusp, preexisting right bundle branch block, narrow left ventricular outflow tract diameters, and severe mitral annulus calcification) [32–34] and procedure-related (depth of implantation of the CoreValve System as well its induced mechanical stress on the aortic valvar complex) factors play a role [33,34]. If true, these findings may lead to improved patient and procedure planning and, more importantly, to changes in implantation technique and guidance in addition to novel delivery catheters and valve technology.

In case of a new PPI, the LOS (median) was 18 days. In this population, 12 patients received a pacemaker within 7 days after TAVI, another 14 patients between 7 and 30 days, and 2 patients received a pacemaker beyond 30 days after TAVI and before hospital discharge. The reason of PPI beyond 7 days after TAVI was postprocedural new-onset conduction disturbances (six patients), logistical issues (four patients), uncertainty and discussion on the indication of PPI (three patients), temporary fever or infection (two patients), and neurocognitive dysfunctional behavior (one patient).

Infections

A high proportion of patients had an infectious complication after TAVI of which urinary tract infection was the most frequent (10%), followed by pulmonary and access site infection (5 and 3%, respectively). Webb et al. [12] found a similar frequency of pulmonary and local infections (4 and 3%, respectively). Measures to avoid urinary tract infection include the early removal of the urinary bladder catheter after TAVI. This is often not possible, because—in our observations—most patients need more time to become fully ambulant as a result of which the urinary catheter remains in situ for a longer period than strictly needed. For patient and staff comfort, we perform TAVI under general anesthesia. Despite the fact that patients are extubated in the catheterization room immediately after the procedure, it is conceivable that anesthesia and ventilation have contributed to the occurrence of pulmonary infection in addition to patient-related factors such as chronic obstructive pulmonary disease. It remains to be seen whether deep sedation and a laryngeal mask reduce pulmonary infections after TAVI.

Length of Stay

There is scant information on length of stay (LOS) after TAVI. The LOS (median) thus far reported in studies that focused on MACCE varies between 5 and 13 days [9,12]. In the absence of a uniform definition of LOS (i.e., in- or excluding time spent in referring hospital after discharge from treating center) and predefined criteria of hospital discharge, it is difficult to compare and interpret these data. Despite this, it is clear that TAVI differs from other catheter-based treatments and that the observed LOS is longer than the one we may have assumed at the initiation of TAVI. This is not surprising given the baseline characteristics of the patients and the nature of TAVI itself and may explain the high frequency of cardiovascular and of the non-cardiovascular complications in this study.

The LOS in octogenarians who underwent surgical AVR with or without combined bypass grafting varies between 7 and 10 days (median) and between 9 and 20 days if expressed as mean [35–38]. Despite the differences in the patients who are selected for surgical AVR and TAVI, the LOS after surgery is noteworthy considering the surgical trauma and the use of cardiopulmonary support during the operation.

Limitation

We concentrated on clinical complications during or after TAVI. Because of limitations in clinical observation, some complications may have remained undetected. The sample size precluded a comprehensive analysis of the independent determinants of complications and LOS, which is needed to improve patient selection and procedure planning. Also, this analysis only reports on the results following treatment with the MCS without a comparison with patients undergoing TAVI with the Edwards–Sapien prosthesis.

CONCLUSIONS

TAVI is associated with a 30-day combined safety endpoint of 22%. At least 1 major adverse event occurred in 51% of the patients; additional PPI was needed in another 8%, and TAVI was truly uncomplicated in 41%. Complications and additional treatment significantly prolonged LOS.

REFERENCES

1. Carroll JD. The evolving treatment of aortic stenosis: Do new procedures provide new treatment options for the highest-risk patients? Circulation 2006;114:533–535.
2. de Jaegere PP, Ruiz C, Bonhoeffer P, Vahanian A, Marco J, Serruys PW. Transcatheter aortic valve implantation. Where are we? EuroIntervention 2009;5:169–171.
3. Thomas M, Wendler O. Transcatheter aortic valve implantation (TAVI): How to interpret the data and what data is required? EuroIntervention 2009;5:25–27.
4. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B, Cribier A, De Jaegere P, Fournial G, Kappetein AP, et al. Transcatheter valve implantation for patients with aortic stenosis: A position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2008;29:1463–1470.
5. Bleiziffer S, Ruge H, Mazzitelli D, Schreiber C, Hutter A, Laborde JC, Bauernschmitt R, Lange R. Results of percutaneous and transapical transcatheter aortic valve implantation performed by a surgical team. Eur J Cardiothorac Surg 2009;35: 615–620.
6. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: Mid-term follow-up from the initial feasibility studies: The French experience. J Am Coll Cardiol 2006;47:1214–1223.
7. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. Progress and current status of percutaneous aortic valve replacement: Results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv 2008;1:167–175.
8. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Walther T, Zickmann B, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: Device success and 30-day clinical outcome. J Am Coll Cardiol 2007; 50:69–76.
9. Himbert D, Descoutures F, Al-Attar N, Iung B, Ducrocq G, Detaint D, Brochet E, Messika-Zeitoun D, Francis F, Ibrahim H, et al. Results of transfemoral or transapical aortic valve implantation following a uniform assessment in high-risk patients with aortic stenosis. J Am Coll Cardiol 2009;54:303–311.
10. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: Results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242–249.
11. Ussia GP, Mule M, Barbanti M, Cammalleri V, Scarabelli M, Imme S, Capodanno D, Ciriminna S, Tamburino C. Quality of life assessment after percutaneous aortic valve implantation. Eur Heart J 2009;30:1790–1796.
12. Webb JG, Altwegg L, Boone RH, Cheung A, Ye J, Lichtenstein S, Lee M, Masson JB, Thompson C, Moss R, et al. Transcatheter aortic valve implantation: Impact on clinical and valve-related outcomes. Circulation 2009;119:3009–3016.
13. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007;116:755–763.
14. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk acute and late outcomes of the multicenter canadian experience. J Am Coll Cardiol 2010;55:1080–1090.
15. Buellesfeld L, Wenaweser P, Gerckens U, Mueller R, Sauren B, Latsios G, Zickmann B, Hellige G, Windecker S, Grube E. Transcatheter aortic valve implantation: Predictors of procedural success—The Siegburg-Bern experience. Eur Heart J 2010;31:984–991.
16. Piazza N, Cutlip DE, Onuma Y, Kappetein AP, de Jaegere P, Serruys PW. Clinical endpoints in transcatheter aortic valve implantation: A call to ARC for standardised definitions. EuroIntervention 2009;5:29–31.
17. Serruys PW. The times, they are a-changing ... constantly! EuroIntervention 2010;5:639–641.
18. Van Mieghem NM, Nuis RJ, Piazza N, Apostolos T, Ligthart J, Schultz C, de Jaegere PP, Serruys PW. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System(R): The Rotterdam experience. EuroIntervention 5:673–679.
19. Leon M, Piazza N, Nikolsky E, Blackstone E, Cutlip D, Kappetein AP, Krucoff M, Mack M, Mehran R, Miller C, et al. 2010. Standardized endpoint definitions for transcatheter aortic valve Implantation Clinical Trials: A Consensus Report from the Valve Academic Research Consortium. Eur Heart J 2010;32:205–217.
20. Tzikas A, Piazza N, van Dalen BM, Schultz C, Geleijnse ML, van Geuns RJ, Galema TW, Nuis RJ, Otten A, Gutierrez-Chico JL, et al. Changes in mitral regurgitation after transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2010;75: 43–49.
21. Piazza N, Onuma Y, de Jaegere P, Serruys PW. Guidelines for reporting mortality and morbidity after cardiac valve interventions—Need for a reappraisal? Ann Thorac Surg 2009;87: 357–358; discussion359–360.
22. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: A diffusion-weighted magnetic resonance imaging study. Circulation 2010;121:870–878.
23. Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: A prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol 2010;55:1427–1432.
24. Gottesman RF, Sherman PM, Grega MA, Yousem DM, Borowicz LM Jr, Selnes OA, Baumgartner WA, McKhann GM. Watershed strokes after cardiac surgery: Diagnosis, etiology, and outcome. Stroke 2006;37:2306–2311.
25. Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM. Neurobehavioural sequelae of cardiopulmonary bypass. Lancet 1999;353:1601–1606.
26. Ducrocq G, Francis F, Serfaty JM, Himbert D, Maury JM, Pasi N, Marouene S, Provenchere S, Iung B, Castier Y, et al. Vascular complications of transfemoral aortic valve implantation with the Edwards SAPIEN prosthesis: Incidence and impact on outcome. EuroIntervention 5:666–672.
27. Kahlert P, Al-Rashid F, Weber M, Wendt D, Heine T, Kottenberg E, Thielmann M, Kuhl H, Peters J, Jakob HG,

et al. Vascular access site complications after percutaneous transfemoral aortic valve implantation. Herz 2009;34: 398–408.
28. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, Soula P, Gabiache Y, Fournial G, Marcheix B, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve(R) bioprostheses in a mixed population. EuroIntervention 2010;5:659–665.
29. Aregger F, Wenaweser P, Hellige GJ, Kadner A, Carrel T, Windecker S, Frey FJ. Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. Nephrol Dial Transplant 2009; 24:2175–2179.
30. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochelliere R, Doyle D, Masson JB, Gutierrez MJ, Clavel MA, Bertrand OF, et al. Acute kidney injury following transcatheter aortic valve implantation: Predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2010;31:865–874.
31. Latsios G, Gerckens U, Buellesfeld L, Mueller R, John D, Yuecel S, Syring J, Sauren B, Grube E. Device landing zone calcification, assessed by MSCT, as a predictive factor for pacemaker implantation after TAVI. Catheter Cardiovasc Interv 2010;76: 431–439.
32. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng GA, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. Am Heart J 2009;157: 860–866.
33. Baan J Jr, Yong ZY, Koch KT, Henriques JP, Bouma BJ, Vis MM, Cocchieri R, Piek JJ, de Mol BA. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. Am Heart J 2010;159:497–503.
34. Piazza N, Nuis R, Tzikas A, Otten A, Onuma Y, García-García H, Schultz C, van Domburg R, van Es G, van Geuns R, et al. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. EuroIntervention 2010;6:475–484.
35. Filsoufi F, Rahmanian PB, Castillo JG, Chikwe J, Silvay G, Adams DH. Excellent early and late outcomes of aortic valve replacement in people aged 80 and older. J Am Geriatr Soc 2008;56:255–261.
36. Kirsch M, Guesnier L, LeBesnerais P, Hillion ML, Debauchez M, Seguin J, Loisance DY. Cardiac operations in octogenarians: Perioperative risk factors for death and impaired autonomy. Ann Thorac Surg 1998;66:60–67.
37. Kolh P, Kerzmann A, Lahaye L, Gerard P, Limet R. Cardiac surgery in octogenarians; peri-operative outcome and long-term results. Eur Heart J 2001;22:1235–1243.
38. Thourani VH, Myung R, Kilgo P, Thompson K, Puskas JD, Lattouf OM, Cooper WA, Vega JD, Chen EP, Guyton RA. Long-term outcomes after isolated aortic valve replacement in octogenarians: A modern perspective. Ann Thorac Surg 2008;86: 1458–1464, discussion1464–1465.

CHAPTER 4

Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System

Effect of Experience on Results of Transcatheter Aortic Valve Implantation Using a Medtronic CoreValve System

Rutger-Jan Nuis, MSc[a], Nicolas M. van Mieghem, MD[a], Robert M. van der Boon, MSc[a], Robert-Jan van Geuns, MD, PhD[a], Carl J. Schultz, MD, PhD[a], Frans B. Oei, MD[b], Tjebbe W. Galema, MD, PhD[a], Goris Bol Raap, MD, PhD[b], Peter J. Koudstaal, MD, PhD[c], Marcel L. Geleijnse, MD, PhD[a], Arie Pieter Kappetein, MD, PhD[b], Patrick W. Serruys, MD, PhD[a], and Peter P. de Jaegere, MD, PhD[a,*]

Outcome after transcatheter aortic valve implantation (TAVI) depends on the patient risk profile, operator experience, progress in technology, and technique. We sought to compare the results of TAVI during the initiation phase and after certification to perform TAVI with the Medtronic CoreValve System without proctoring. A total of 165 consecutive patients was categorized into a first cohort of 33 patients treated before certification (November 2005 to December 2007) and a second cohort of 132 patients treated after certification (January 2008 to October 2010). The study end points were selected and defined according to the Valve Academic Research Consortium recommendations. Compared to cohort 2, the patients in cohort 1 more frequently had New York Heart Association class III–IV (100% vs 71%, p <0.001), hypertension (67% vs 39%, p = 0.004), and aortic regurgitation grade III–IV (46% vs 22%, p = 0.006) before TAVI. Over time, the patients in cohort 2 more frequently underwent a truly percutaneous approach (98% vs 82%, p = 0.002) without circulatory support (96% vs 67%, p <0.001) but with more concomitant percutaneous coronary intervention (11% vs 0%, p = 0.042) than the patients in cohort 1. They also more often received a 29-mm prosthesis (72% vs 24%, p <0.001), required less postimplantation balloon dilation (10% vs 27%, p = 0.008), and had less aortic regurgitation grade III–IV after TAVI (12% vs 30%, p = 0.010). The clinical outcome showed a nonsignificant reduction in the combined safety end point (30% to 17%) but a significant reduction in cerebrovascular events (21% to 7%, p = 0.020) and life-threatening bleeding (15% to 5%, p = 0.044) in cohort 2. However, the reduction in overall bleeding and vascular complications (25% and 14%, respectively) was not significant. In conclusion, TAVI became significantly less complex and was associated with better results over time but remained associated with a high frequency of periprocedural major cardiovascular complications. **(Am J Cardiol 2011;107:1824–1829)**

Compared to patients who underwent transcatheter aortic valve implantation (TAVI) in the early days, patients treated later have been reported to benefit from improved procedural success rates, with subsequent improved survival.[1] The developments of smaller delivery catheters, improvements in frame technology, and increased operator experience, in addition to changes in the baseline risk of patients, have played a role. In the present study, we describe the effect of our experience, in addition to changes in patient demographics, procedure, and outcome of TAVI with the Medtronic CoreValve System (MCS), in a cohort treated before (2005 to 2007) and after (January 2008) certification to perform TAVI as a solo center.

Methods

From November 2005 to October 2010, 165 consecutive patients with severe aortic stenosis underwent TAVI with the MCS. All patients were accepted for TAVI by Heart Team consensus by a cardiologist and cardiac surgeon who agreed that surgical aortic valve replacement was associated with a too high or prohibitive risk, using previously reported criteria.[2] The treatment decision was made on the basis of a comprehensive analysis of symptoms, physical examination findings, laboratory assessment, 12-lead electrocardiographic findings, 2-dimensional transthoracic echocardiography, including continuous pulsed wave Doppler examination of the aortic valve for calculation of the aortic valve area and mean gradient according to the recommendations of the American Society of Echocardiography, and assessment of the coronary and peripheral arteries by angiography or MSCT.[3,4]

Departments of [a]Cardiology, [b]Cardio-Thoracic Surgery, and [c]Neurology, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received December 13, 2010; manuscript received and accepted February 12, 2011.

*Corresponding author: Tel: (00) 311-0703-1763; fax: (00) 311-0703-4320.

E-mail address: p.dejaegere@erasmusmc.nl (P.P. de Jaegere).

Table 1
Baseline patient characteristics stratified by cohort

Variable	Entire Cohort (n = 165)	Cohort 1* (n = 33)	Cohort 2* (n = 132)	p Value
Age (years)	81 ± 8	82 ± 7	80 ± 8	0.39
Men	75 (46%)	15 (46%)	60 (46%)	1.0
Height (cm)	167 ± 9	167 ± 8	167 ± 9	0.86
Weight (kg)	73 ± 13	73 ± 13	72 ± 13	0.77
Body mass index (kg/m^2)	26.0 ± 4.0	26.2 ± 4.6	26.0 ± 3.8	0.77
Body surface area (m^2)	1.83 ± 0.19	1.84 ± 0.19	1.83 ± 0.20	0.83
New York Heart Association class ≥III	127 (77%)	33 (100%)	94 (71%)	<0.001
Previous cerebrovascular event	35 (21%)	8 (24%)	27 (21%)	0.63
Previous myocardial infarction	43 (26%)	7 (21%)	36 (27%)	0.48
Previous coronary artery bypass graft surgery	42 (26%)	10 (30%)	32 (24%)	0.48
Previous percutaneous coronary intervention	46 (28%)	8 (24%)	38 (29%)	0.60
Diabetes mellitus	38 (23%)	8 (24%)	30 (23%)	0.85
Hypertension	73 (44%)	22 (67%)	51 (39%)	0.004
Glomerular filtration rate <60 ml/min	90 (55%)	20 (61%)	70 (53%)	0.43
Chronic hemodialysis	8 (5%)	2 (6%)	6 (5%)	1.0
Chronic obstructive pulmonary disease	45 (27%)	7 (21%)	38 (29%)	0.89
Permanent pacemaker	26 (16%)	5 (15%)	21 (16%)	0.89
Atrial fibrillation	40 (25%)	7 (21%)	33 (25%)	0.62
Aortic valve annulus (mm)	22.6 ± 2.2	22.7 ± 2.3	22.6 ± 2.2	0.97
Aortic valve area (cm^2)	0.64 ± 0.21	0.67 ± 0.17	0.63 ± 0.22	0.34
Mean aortic gradient	45 ± 17	48 ± 19	45 ± 16	0.38
Aortic regurgitation grade III or greater	44 (27%)	15 (46%)	29 (22%)	0.006
Mitral regurgitation grade III or greater	23 (14%)	7 (21%)	16 (21%)	0.18
Logistic European System for Cardiac Operative Risk Evaluation	13.1 (9.8–19.4)	14.2 (10.5–18.7)	12.6 (9.6–21.2)	0.53
Society of Thoracic Surgeons' score	4.6 (3.3–6.7)	5.3 (3.0–8.0)	4.6 (3.3–6.3)	0.28

Data are expressed as mean ± SD, median (interquartile range), or number of patients (%).
* Cohort 1 and 2 included patients treated before (n = 33) and after (n = 132) institutional qualification and certification in January 2008 to perform TAVI as a solo center without additional assistance of a proctor, respectively.

During the study period, 322 patients were screened, for whom the acceptance rate for TAVI increased from 23% in 2006 to 76% in 2009. The patients agreed to TAVI in writing.

The details of the device and the procedure have been previously reported.[5,6] The first 5 patients underwent TAVI with the second-generation MCS, which is implanted using a 21Fr delivery catheter inserted into the common femoral (n = 4) or the subclavian (n = 1) artery using surgical exposure without the use of an arterial sheath. All other patients underwent TAVI with the third-generation MCS, which is delivered using an 18Fr arterial sheath inserted into the femoral artery using an echocardiographic-guided Seldinger technique and closure with a 10Fr Prostar[7] (Prostar XL, Abbott Vascular, Illinois); except for 4 who underwent the subclavian approach. All patients underwent general anesthesia, and valve implantation was done using cine and fluoroscopic guidance.

The preprocedural demographic, clinical, laboratory, and technical (electrocardiographic and echocardiographic) data were prospectively collected and entered in a dedicated database. Transthoracic echocardiography was performed 1 day before the procedure and within 7 days after TAVI. The details of the analysis have been previously reported.[7] The Valve Academic Research Consortium recommendations were used for all separate and composite end points in the present study.[8] The following separate clinical end points were collected during or immediately after TAVI: death, myocardial infarction, cerebrovascular complications, vascular and bleeding complications, and acute kidney injury (AKI). The following prosthetic valve associated end points were recorded: new left bundle branch block, new third-degree atrioventricular block, new permanent pacemaker implantation, and coronary obstruction. Finally, the therapy-specific end points were recorded, including ventricular perforation at any point resulting in cardiac tamponade, postimplantation balloon dilation, valve-in-valve implantation, and unplanned cardiopulmonary bypass with or without conversion to open surgical aortic valve replacement. All cerebrovascular events were evaluated and adjudicated by a vascular neurologist who reassessed such patients daily. The serum creatinine results ≤72 hours after the procedure were collected to identify the patients with AKI, and data on the red blood cell transfusions were recorded by our institution's blood bank laboratory. Twelve-lead electrocardiographic recordings were obtained 1 day before treatment and 1 day after treatment, after which the electrocardiograms were examined by an independent cardiologist for the occurrence of new left bundle branch block.

To assess the effect of the experience on clinical outcome, the study population was divided into 2 patient cohorts. Cohort 1 (C-1) included the initial 33 patients treated from November 2005 to December 2007. Cohort 2 (C-2) included the subsequent 132 patients who were treated from January 2008 to October 2010. This distinction in time was made by receipt of certification in January 2008, attesting that our institution and team were qualified to perform TAVI without any additional assistance or the presence of a

Table 2
Procedural details and results stratified by cohort

Variable	Cohort 1 (n = 33)	Cohort 2 (n = 132)	p Value
Vascular access			
Surgical—femoral artery	4 (12%)	0	0.001
Surgical—subclavian artery	2 (6%)	3 (2%)	0.59
Percutaneous—femoral artery	27 (82%)	128 (98%)	0.002
Circulatory support*			
Extracorporeal membrane oxygenation	2 (6%)	1 (1%)	0.10
Left ventricular assist device	9 (27%)	4 (3%)	<0.001
None	22 (67%)	126 (96%)	<0.001
Additional interventions during procedure			
Percutaneous transluminal angioplasty iliac artery	3 (9%)	2 (2%)	0.055
Percutaneous coronary intervention	0	15 (11%)	0.042
Prosthesis size† (mm)			
26	25 (76%)	36 (28%)	<0.001
29	8 (24%)	94 (72%)	<0.001
Therapy-specific results			
Ventricular perforation resulting in cardiac tamponade	1 (3%)	0	1.0
Postimplantation balloon dilation	9 (27%)	13 (10%)	0.008
Valve-in-valve implantation	3 (9%)	5 (4%)	0.36
Unplanned cardiopulmonary bypass use	0	0	1.0
Conversion to open surgical aortic valve replacement	0	0	1.0
Contrast volume (ml)	211 ± 71	176 ± 83	0.041
Duration of procedure (min)	230 ± 74	257 ± 80	0.099

Data are expressed as mean ± SD or number of patients (%).
* One patient died during induction of anesthesia.
† Two patients did not receive a valve (1 death during induction of anesthesia and 1 death after balloon valvuloplasty).

Table 3
In-hospital clinical outcome, prosthetic-valve associated outcome, and echocardiographic findings stratified by cohort*

Variable	Cohort 1 (n = 33)	Cohort 2 (n = 132)	p Value
In-hospital clinical outcome			
Thirty day or in-hospital death			
All-cause	1 (3%)	15 (11%)	0.20
Cardiovascular cause	1 (3%)	10 (8%)	0.47
Periprocedural myocardial infarction (<72 hours)	1 (3%)	0	0.20
Spontaneous myocardial infarction (>72 hours)	0	0	1.0
Cerebrovascular complication	7 (21%)	9 (7%)	0.020
Major stroke	3 (9%)	7 (5%)	0.69
Minor stroke	0	1 (1%)	1.0
Transient ischemic attack	4 (12%)	1 (1%)	0.006
Vascular complication	6 (18%)	19 (14%)	0.59
Major	3 (9%)	7 (5%)	0.69
Minor	3 (9%)	12 (9%)	1.0
Bleeding complication <24 hours	8 (24%)	33 (25%)	0.95
Life-threatening or disabling	5 (15%)	6 (5%)	0.044
Major	3 (9%)	18 (14%)	0.48
Minor	0	9 (7%)	0.12
Bleeding complication >24 hours	2 (6%)	6 (5%)	1.0
Life-threatening or disabling	1 (3%)	3 (2%)	1.0
Major	0	3 (2%)	0.61
Minor	1 (3%)	0	0.20
Acute kidney injury	9 (27%)	18 (14%)	0.056
Stage 1	6 (18%)	15 (11%)	0.38
Stage 2	1 (3%)	2 (2%)	1.0
Stage 3	2 (6%)	1 (1%)	0.10
In-hospital reintervention	0	2 (2%)	1.0
Combined safety end point at 30 days†	10 (30%)	22 (17%)	0.076
Prosthetic-valve associated outcome			
Conduction disturbances			
Left bundle branch block	14 (42%)	61 (46%)	0.70
Pacemaker for third-degree atrioventricular block	4 (12%)	18 (14%)	0.58
Pacemaker for other than third-degree atrioventricular block	2 (6%)	5 (4%)	0.63
Coronary obstruction	1 (3%)	0	0.20
Echocardiography results			
Aortic valve area (cm^2)	1.69 ± 0.53	1.76 ± 0.55	0.60
Mean aortic gradient	11 ± 6	9 ± 3	0.013
Aortic regurgitation grade III or greater	10 (30%)	16 (12%)	0.010
Mitral regurgitation grade III or greater	6 (18%)	14 (10%)	0.24

Data are expressed as mean ± SD or number of patients (%).
* Mutually nonexclusive analysis (≥1 event/patient possible).
† Composite all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury (stage 3), periprocedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional).

proctor. Also, 2005 to 2007 constituted the period during which TAVI evolved from a hybrid surgical approach with cardiopulmonary support to a truly percutaneous procedure (October 2006), with the gradual omission of circulatory support (December 2006).

The preprocedural, procedural, and in-hospital results were compared between the 2 groups. The categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test. The normal and skewed continuous variables are presented as the mean ± SD and median (interquartile range), respectively. A comparison of the continuous variables was done using the Student *t* test or Wilcoxon rank sum test. Two-sided p values <0.05 were considered to indicate significance. All statistical analyses were performed using the Statistical Package for Social Sciences software, version 17.0 (SPSS, Chicago, Illinois).

Results

The baseline patient characteristics and procedural details of the entire population and the 2 cohorts are listed in Tables 1 and 2, respectively. Compared to the C-2 patients, the C-1 patients were more symptomatic (New York Heart Association class III or IV, 100% vs 71%, p <0.001), more frequently had a history of hypertension (67% vs 39%, p = 0.004), and more often presented with aortic regurgitation grade III or greater (46% vs 22%, p = 0.006).

The C-2 patients more frequently underwent a truly per-

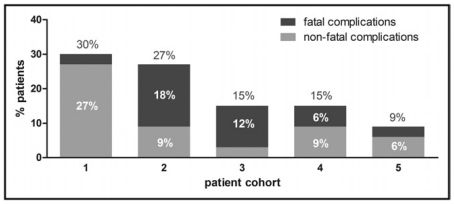


Figure 1. Frequencies of combined safety end point at 30 days stratified by fatal and nonfatal complications according to 5 subsequent patient cohorts of 33 patients each. Safety end point at 30 days included composite all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury (stage 3), periprocedural myocardial infarction, repeat procedure for valve-related dysfunction (surgical or interventional).

cutaneous transfemoral approach (98% vs 82%, p = 0.002) without circulatory support (96% vs 67%, p <0.001) but more often underwent concomitant percutaneous coronary intervention during the TAVI procedure (11% vs 0%, p = 0.042). Because the 29-mm inflow valve became available in October 2007, a smaller proportion of C-1 patients received a 29-mm inflow valve (24% vs 72%, p <0.001). Thus, additional balloon dilation immediately after valve implantation was used less often in the C-2 patients (10% vs 27%, p = 0.008). The TAVI procedures in C-2 were also characterized by a reduced use of contrast media (176 vs 211 ml, p = 0.041).

A trend was seen toward an increase in all-cause mortality over time (3% to 11%). The time and cause of death in the 15 patients in C-2 were as follows; 3 intraprocedural (induction of anesthesia, left ventricular outflow tract rupture, and electromechanical dissociation in 1 each), 11 in-hospital (major stroke in 3, heart failure in 2, sepsis in 2, pneumonia in 2, asystole in 1, and pneumothorax during permanent pacemaker implantation in 1), and 1 sudden death immediately after discharge. Despite this, a trend was seen toward a reduction of the combined safety end point at 30 days from 30% to 17% (Table 3). The latter was predominantly caused by a reduction in life-threatening bleeding events occurring during or immediately after TAVI (15% to 5%, p = 0.044). However, a significant reduction occurred in cerebrovascular complications (21% to 7%, p = 0.020), mainly because of a reduction in transient ischemic attacks (12% to 1%, p = 0.006). Computed tomography of the brain was performed in all patients who experienced a major or minor stroke and revealed that the cause of the insult was ischemic in origin (embolus) in 81% and due to hemodynamic changes during the procedure (watershed) in 19% of the patients.

To address the limitations of a breakdown of the population into 2 unequally sized groups, the population of 165 patients was also categorized in 5 succeeding subgroups of 33 patients (Figure 1). A clear reduction in clinical complication rates over time was observed.

From a technical viewpoint, the C-2 patients had a lower mean aortic valve gradient (9 vs 11 mm Hg, p = 0.013) and less frequently had aortic regurgitation grade III or greater (12% vs 30%, p = 0.010) at the predischarge echocardiographic Doppler analysis comparison to the C-1 patients.

Discussion

We found that in the function of time, the patients treated later were at a somewhat lower risk than those treated during the initiation period and that the procedure became less invasive and complex by avoiding circulatory support, although TAVI was more often combined with percutaneous coronary intervention in the later series. In terms of outcome, we observed an important improvement in safety according to the Valve Academic Research Consortium safety end point, mainly because of a reduction in life-threatening periprocedural bleeding complications. Also a significant reduction in transient ischemic attacks occurred. From a procedural perspective, postimplantation balloon dilation was less often performed in the C-2 patients and they also had a lower incidence of aortic regurgitation grade III or greater after TAVI.

This summary of findings was based on an analysis of 165 consecutive patients with a breakdown of these patients into 2 groups; those treated during the initiation and development period (November 2005 to December 2007) and those treated after January 2008 when the TAVI certification was obtained. The number of patients obviously affects the robustness of these findings because 1 event more or less in 1 group—in particular in C-1—could result in different findings. However, when we analyzed the combined safety end point at 30 days using 5 consecutive groups of 33 patients each, a substantial, and almost linear, reduction in the complication rates was seen as a function of time (Figure 1).

With respect to the patient characteristics, the change in profile can be explained by the natural evolution of an initially experimental clinical program and treatment. At variance with percutaneous coronary intervention, TAVI was initiated in patients who were rejected for surgery or who were poor surgical candidates. The tendency of selecting less sick patients over time might not, therefore, be surprising. To keep pace with the reality of clinical practice, it is worth mentioning that planned randomized studies such as the SURgery and transcatheter Aortic Valve Implantation (SURTAVI) trial will enroll patients with a risk profile less than the current criteria of eligibility for TAVI.[9] The baseline risk is currently most often expressed by the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) or Society of Thoracic Surgeons' score. Given the skewed distribution of the individual characteristics of the patients who undergo TAVI, we used the median and interquartile range and not the mean values of these scores. This explains why our reported values of 14.2% (interquartile range 10.5% to 18.7%) and 5.3% (interquartile range 3.0% to 8.0%) were somewhat lower than those reported in other studies.[1,5,10,11] Also, differences in the interpretation of the definitions of the variables that must be entered in the risk model could play a role. When examining the individual patient characteristics between this population and those of the published observational studies reported, few differences were seen.[1,5,10,11] Because the limitations of risk models are widely recognized,[12] the

Heart Team discussion and consensus in treatment decision and allocation has been gaining weight and importance in clinical practice and studies.[9]

Not unexpectedly, the procedure substantially changed as a function of time. The first patient was treated in November 2005, barely 1 year after the first transfemoral TAVI in April 2004. At that time, all TAVI procedures with the MCS were performed with the 25Fr or 21Fr sheathless delivery catheter and implied surgical cutdown of the femoral artery. Also, at that stage, it was believed that circulatory support was required during TAVI. As the experience and insights into the procedure increased, it became clear that this was not the case. Also, a reduction in the delivery catheter size allowed a true percutaneous approach (October 2007) followed by the advent of a 29-mm inflow MCS that, similar to the 26-mm inflow MCS, can be delivered with an 18Fr delivery catheter. Regarding the arterial access, only a few subclavian procedures were performed. A more direct access to the heart by way of the subclavian artery or direct aortic access can be advantageous, given the superiority of surgical hemostasis in comparison to the percutaneous techniques and better valve positioning owing to the improved catheter response while positioning, which, in turn, can lead to fewer conduction abnormalities.[13–15]

This series does not allow a precise definition of the factors that most contributed to the improvement in clinical outcome as a function of time. The changes in the baseline risk of the patients, improvements in the technology and procedure (18Fr instead of 21Fr delivery catheter), omission of circulatory support, increased experience of the operators, and improvements in postoperative care (e.g., lower threshold for radiologic examination in the case of oozing at the access site) could have played a role. When excluding the first 5 patients who were treated with the 21Fr delivery catheter, we found that the combined safety end point in C-1 decreased by only 2%. In addition, we believe that the continuous improvement can more likely be explained by the increasing operator/institutional experience, and not the reduction in the size of the delivery catheter, although the latter was invariably associated with an increased risk of bleeding and vascular complications. Regarding the use of circulatory support systems, it should be acknowledged that in addition to their potential risks (e.g., bleeding-vascular complications, AKI), these systems can have had a protective role, as well, especially in the early phase, or in patients with poor left ventricular function.

We found no differences in the total frequency of bleeding and vascular complications in our series. Depending on the accuracy of observation and the definition used, the reported incidence of these complications in the published data has varied from 4% to 32%.[16–18] According to the Valve Academic Research Consortium consensus that proposes the number of red blood cell transfusion as a measure of bleeding severity, bleeding complications were less severe in patients treated later because fewer transfusions (1.1 vs 2.1 U, $p = 0.007$) were needed. All patients who required additional surgical or interventional treatment because of bleeding or vascular complications were related to incomplete femoral artery closure with the Prostar device. This high rate of failure of hemostasis should not be surprising, because the Prostar closure device is proposed for vascular puncture holes $<$10Fr only.[19] It is, therefore, logical that some centers prefer a limited surgical cutdown of the femoral artery, instead of "off label" use of a closure device.[20]

We did not observe a reduction in all-cause and cardiovascular mortality. The cardiovascular mortality rate varied from 3% to 8% in the present study and was comparable to the mortality reported in observational studies and in the Placement of AoRTic TraNscathetER Valve Trial (PARTNER) trial (5%).[10,11,21] The most striking improvement was the reduction in transient ischemic attacks. Whether this can be attributed to improved operator skills of catheter handling and valve positioning is unknown. A major stroke occurred in 9% of the C-1 patients and in 5% of the C-2 patients. The latter, also, is in accordance with the data from observational studies and the PARTNER trial (5%). Although most of these accidents were of presumed cardioembolic origin, some were lacunar and resulted from cerebral small vessel disease and not embolism. A better understanding of the etiology is needed to improve patient selection and procedure planning and execution. For instance, the prevalence of hypertension, an established predictor of stroke after cardiac surgery, was significantly less in C-2 than in C-1.[22]

AKI is recognized to be associated with poor survival after cardiac interventions, including percutaneous coronary intervention, cardiac surgery, and TAVI and, thus, highlights the importance of its avoidance or prevention.[23–26] This is particularly true for patients who undergo TAVI, given the high prevalence of pre-existing impaired renal function.[25,26] In the present series, we found a reduction of almost 50%, which can in part be explained by patient variables such as a greater prevalence of antecedent hypertension in the C-1 patients. Compared to the C-2 patients, the C-1 patients had a greater risk of AKI, owing to the more frequent use of circulatory support, more severe bleeding, potentially inducing renal ischemia, more frequent administration of red blood cell transfusions $<$24 hours (2.1 vs 1.1 U, $p = 0.007$), and, last, but not least, the greater volumes of contrast administration (211 vs 176 ml, $p = 0.041$).

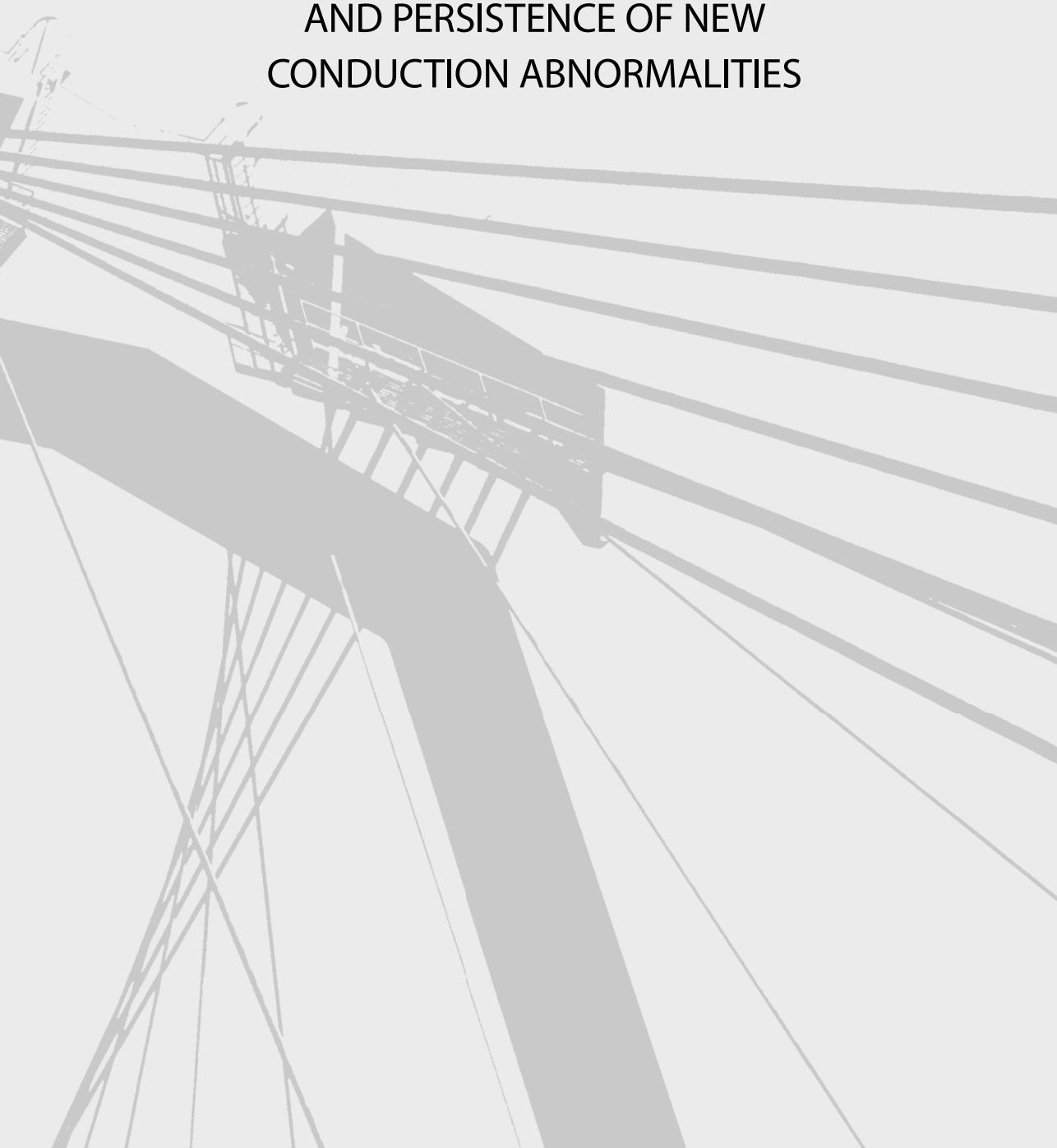
We did not observe a reduction in the occurrence of left bundle branch block or third-degree atrioventricular block after TAVI. The pathophysiology of these new conduction abnormalities is complex. A number of studies have indicated that both patient- and procedure-related variables, such as the septal wall thickness, the noncoronary cusp thickness, pre-existing right bundle branch block, the depth of implantation within the left ventricular outflow tract, and postimplant prosthesis expansion, in addition to the type of prosthesis, are associated with new left bundle branch block or permanent pacemaker implantation.[27–29] From a procedural viewpoint, it is conceivable that better valve size selection and positioning will lead to fewer conduction abnormalities.

1. Webb J, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere R, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein S. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007;116:755–763.
2. Otten AM, van Domburg RT, van Gameren M, Kappetein AP, Takkenberg JJ, Bogers AJ, Serruys PW, de Jaegere PP. Population characteristics, treatment assignment and survival of patients with aortic

stenosis referred for percutaneous valve replacement. *EuroIntervention* 2008;4:250–255.
3. Schiller NB, Shah PM, Crawford M, De Maria A, Devereux R, Feigenbaum H, Gutgesell H, Reicheck N, Sahn D, Schnittger I, Silverman NH, Tajik AJ; American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. *J Am Soc Echocardiogr* 1989;2:358–367.
4. Schultz C, Moelker A, Piazza N, Tzikas A, Otten A, Nuis R, Neefjes L, van Geuns R, de Feyter P, Krestin G, Serruys P, de Jaegere P. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J* 2010;31:849–856.
5. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. *Circ Cardiovasc Interv* 2008;1:167–175.
6. de Jaegere P, van Dijk L, Laborde J, Sianos G, Orellana Ramos F, Lighart J, Kappetein A, Vander Ent M, Serruys P. True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, prostar(R) XL and the TandemHeart(R). *EuroIntervention* 2007;2:500–505.
7. Tzikas A, Piazza N, van Dalen B, Schultz C, Geleijnse M, van Geuns R, Galema T, Nuis R, Otten A, Gutierrez-Chico J, Serruys P, de Jaegere P. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;75:43–49.
8. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials a consensus report from the valve academic research consortium. *J Am Coll Cardiol* 2011;57:253–269.
9. Serruys PW. Design of a novel randomized clinical trial comparing SAVR with TAVI in patients with severe aortic stenosis at intermediate peri-operative risk. Presented at TCT Congress, September 21, 2010, Washington. Available at: *www.tctmd.com*. Accessed on September 21, 2010.
10. Webb J, Chandavimol M, Thompson C, Ricci D, Carere R, Munt B, Buller C, Pasupati S, Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842–850.
11. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson W, Wendler O. Thirty-day results of the SAPIEN aortic bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2010;122:62–69.
12. Brown ML, Schaff HV, Sarano ME, Li Z, Sundt TM, Dearani JA, Mullany CJ, Orszulak TA. Is the European System for Cardiac Operative Risk Evaluation model valid for estimating the operative risk of patients considered for percutaneous aortic valve replacement? *J Thorac Cardiovasc Surg* 2008;136:566–571.
13. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, Ramondo A, Ussia GP, Ettori F, Poli A, Brambilla N, Saia F, De Marco F, Colombo A. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv* 2010;3:359–366.
14. Bapat V, Thomas M, Hancock J, Wilson K. First successful transcatheter aortic valve implantation through ascending aorta using Edwards SAPIEN THV system. *Eur J Cardiothorac Surg* 2010;38:811–813.
15. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly "no-access option" patients. *Catheter Cardiovasc Interv* 2010;75:1129–1136.
16. Van Mieghem N, Nuis R, Piazza N, Apostolos T, Ligthart J, Schultz C, de Jaegere P, Serruys P. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. *EuroIntervention* 2010;5:673–679.
17. Kahlert P, Al-Rashid F, Weber M, Wendt D, Heine T, Kottenberg E, Thielmann M, Kühl H, Peters J, Jakob H, Sack S, Erbel R, Eggebrecht H. Vascular access site complications after percutaneous transfemoral aortic valve implantation. *Herz* 2009;34:398–408.
18. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, Soula P, Gabiache Y, Fournial G, Marcheix B, Carrie D, Fajadet J. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. *EuroIntervention* 2010;5:659–665.
19. Baim D, Knopf W, Hinohara T, Schwarten D, Schatz R, Pinkerton C, Cutlip D, Fitzpatrick M, Ho K, Kuntz R. Suture-mediated closure of the femoral access site after cardiac catheterization: results of the suture to ambulate and discharge (STAND I and STAND II) trials. *Am J Cardiol* 2000;85:864–869.
20. Morasch M, Kibbe M, Evans M, Meadows W, Eskandari M, Matsumura J, Pearce W. Percutaneous repair of abdominal aortic aneurysm. *J Vasc Surg* 2004;40:12–16.
21. Leon M, Smith C, Mack M, Miller D, Moses J, Svensson L, Tuzcu E, Webb J, Fontana G, Makkar R, Brown D, Block P, Guyton R, Pichard A, Bavaria J, Herrmann H, Douglas P, Petersen J, Akin J, Anderson W, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
22. Bucerius J, Gummert J, Borger M, Walther T, Doll N, Onnasch J, Metz S, Falk V, Mohr F. Stroke after cardiac surgery: a risk factor analysis of 16,184 consecutive adult patients. *Ann Thorac Surg* 2003;75:472–478.
23. Rihal C, Textor S, Grill D, Berger P, Ting H, Best P, Singh M, Bell M, Barsness G, Mathew V, Garratt K, Holmes DJ. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105:2259–2264.
24. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann L, Druml W, Bauer P, Hiesmayr M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *J Am Soc Nephrol* 2004;15:1597–1605.
25. Bagur R, Webb J, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson J, Gutiérrez M, Clavel M, Bertrand O, Pibarot P, Rodés-Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. *Eur Heart J* 2010;31:865–874.
26. Nuis RJ, van Mieghem NM, Tzikas A, Piazza N, Otten AA, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* Epub 2010 Nov 8.
27. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng G, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;157:860–866.
28. Bleiziffer S, Ruge H, Hörer J, Hutter A, Geisbüsch S, Brockmann G, Mazzitelli D, Bauernschmitt R, Lange R. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;3:524–530.
29. Piazza N, Nuis R, Tzikas A, Otten A, Onuma Y, García-García H, Schultz C, van Domburg R, van Es G, van Geuns R, de Jaegere P, Serruys P. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. *EuroIntervention* 2010;6:475–484.

PART 2

FREQUENCY, PATHOPHYSIOLOGY AND PERSISTENCE OF NEW CONDUCTION ABNORMALITIES



CHAPTER 5

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

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

Rutger-Jan Nuis, Nicolas M. Van Mieghem, Carl J. Schultz, Apostolos Tzikas, Robert M. Van der Boon, Anne-Marie Maugenest, Jin Cheng, Nicolo Piazza, Ron T. van Domburg, Patrick W. Serruys, and Peter P. de Jaegere*

Department of Cardiology, Erasmus Medical Centre, Rotterdam, The Netherlands

Received 6 January 2011; revised 28 February 2011; accepted 20 March 2011

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.

Conclusion 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.

Keywords Transcatheter aortic valve implantation • Conduction abnormalities • Pacemaker • Timing

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[1–5] and to vary between 6 and 18%, 0 and 27%, and 0 and 27%, respectively, after the implantation of the EDWARDS Sapien valve.[6–9]

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 predefined 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 220 b.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 ($\pm$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

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

	Entire cohort ($n = 65$)	New CAs ($n = 53$)	No new CAs ($n = 12$)	*P*-value
Baseline patient characteristics				
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 coronary artery bypass graft surgery, *n* (%)	12 (19)	9 (17)	3 (25)	0.68
Previous percutaneous coronary intervention, *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

ACE, angiotensin-converting enzyme; CAs, conduction abnormalities; NYHA, New York Heart Association.

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 ($P = 0.35$). 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

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)
Echocardiography	
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)

AV3B, third-degree atrioventricular block; CAs, conduction abnormalities; LBBB, left bundle branch block; RBBB, right bundle branch block.
[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.

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).

Table 4 summarizes potential determinants of new CAs during balloon valvuloplasty (phase 3) and during valve implantation

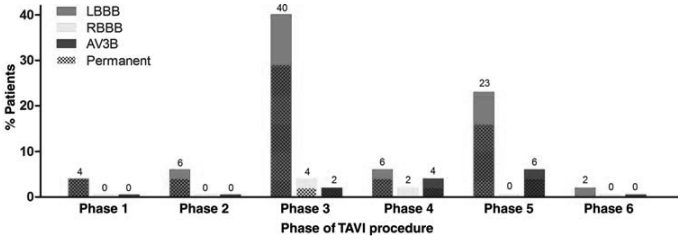


Figure 1 Distribution of first occurrence of new CAs (LBBB, RBBB, and AV3B) per phase of TAVI and associations with permanent change as identified on discharge ECG among a total of 48 patients with new CAs during TAVI. The frequencies of first appearance of new CAs (=LBBB, RBBB, and/or AV3B) on the continuous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

CAs, conduction abnormalities.

(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 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.*[12] recently reported an association between balloon size and the occurrence of new-onset AV3B requiring PPI after TAVI. 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.*,[8] who studied 33 patients who underwent transapical TAVI, we found no relationship between the valve size/aortic annulus ratio and new CAs. 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. 10.39×10^9/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.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: P.P. de Jaegere is proctor for Medtronic; N.P. is a consultant for Medtronic; all other authors have nothing to declare.

References

1. Baan JJ, Yong Z, Koch K, Henriques J, Bouma B, Vis M, Cocchieri R, Piek J, de Mol B. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. *Am Heart J* 2010;**159**:497–503.
2. Roten L, Wenaweser P, Delacrétaz E, Hellige G, Stortecky S, Tanner H, Pilgrim T, Kadner A, Eberle B, Zwahlen M, Carrel T, Meier B, Windecker S. Incidence and predictors of atrioventricular conduction impairment after transcatheter aortic valve implantation. *Am J Cardiol* 2010;**106**:1473–1480.
3. Erkapic D, Kim W, Weber M, Möllmann H, Berkowitsch A, Zaltsberg S, Pajitnev D, Rixe J, Neumann T, Kuniss M, Sperzel J, Hamm C, Pitschner H. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace* 2010;**12**:1188–1190.
4. Piazza N, Nuis R, Tzikas A, Otten A, Onuma Y, García-García H, Schultz C, van Domburg R, van Es G, van Geuns R, de Jaegere P, Serruys P. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. *EuroIntervention* 2010;**6**:475–484.
5. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, Laborde J, de Jaegere P, Serruys P. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. *EuroIntervention* 2008;**4**:242–249.
6. Leon M, Smith C, Mack M, Miller D, Moses J, Svensson L, Tuzcu E, Webb J, Fontana G, Makkar R, Brown D, Block P, Guyton R, Pichard A, Bavaria J, Herrmann H, Douglas P, Petersen J, Akin J, Anderson W, Wang D, Pocock S, PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;**363**:1597–1607.
7. Sinhal A, Altwegg L, Pasupati S, Humphries K, Allard M, Martin P, Cheung A, Ye J, Kerr C, Lichtenstein S, Webb J. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *JACC Cardiovasc Interv* 2008;**1**:305–309.
8. Gutiérrez M, Rodés-Cabau J, Bagur R, Doyle D, DeLarochellière R, Bergeron S, Lemieux J, Villeneuve J, Côté M, Bertrand O, Poirier P, Clavel M, Pibarot P, Dumont E. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;**158**:302–308.
9. Thielmann M, Wendt D, Eggebrecht H, Kahlert P, Massoudy P, Kamler M, Erbel R, Jakob H, Sack S. Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. *Ann Thorac Surg* 2009;**88**:1468–1474.
10. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng G, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;**157**:860–866.
11. Ferreira N, Caeiro D, Adão L, Oliveira M, Gonçalves H, Ribeiro J, Teixeira M, Albuquerque A, Primo J, Braga P, Simões L, Ribeiro V. Incidence and predictors of permanent pacemaker requirement after transcatheter aortic valve implantation with a self-expanding bioprosthesis. *Pacing Clin Electrophysiol* 2010;**33**:1364–1372.
12. Bleiziffer S, Ruge H, Hörer J, Hutter A, Geisbüsch S, Brockmann G, Mazzitelli D, Bauernschmitt R, Lange R. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. *JACC Cardiovasc Interv* 2010;**3**:524–530.
13. Piazza N, Onuma Y, Jesserun E, Kint P, Maugenest A, Anderson R, de Jaegere P, Serruys P. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv* 2008;**1**:310–316.
14. Haworth P, Behan M, Khawaja M, Hutchinson N, de Belder A, Trivedi U, Laborde J, Hildick-Smith D. Predictors for permanent pacing after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;**76**:751–756.
15. Leon M, Piazza N, Nikolsky E, Blackstone E, Cutlip D, Kappetein AP, Krucoff M, Mack M, Mehran R, Miller C, Morel M-A, Petersen J, Popma J, Takkenberg J, Vahanian A, van Es G-A, Vranckx P, Webb J, Windecker S, Serruys P. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Eur Heart J* 2011;**32**:205–217.
16. Willems J, Robles de Medina E, Bernard R, Coumel P, Fisch C, Krikler D, Mazur N, Meijler F, Mogensen L, Moret P. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. *J Am Coll Cardiol* 1985;**5**:1261–1275.
17. Schultz C, Moelker A, Piazza N, Tzikas A, Otten A, Nuis R, Neefjes L, van Geuns R, de Feyter P, Krestin G, Serruys P, de Jaegere P. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J* 2010;**31**:849–856.
18. Piazza N, de Jaegere P, Schultz C, Becker A, Serruys P, Anderson R. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Interv* 2008;**1**:74–81.
19. Godino C, Maisano F, Montorfano M, Latib A, Chieffo A, Michev I, Al-Lamee R, Bande M, Mussardo M, Arioli F, Ielasi A, Cioni M, Taramasso M, Arendar I, Grimaldi A, Spagnolo P, Zangrillo A, La Canna G, Alfieri O, Colombo A. Outcomes after transcatheter aortic valve implantation with both Edwards-SAPIEN and CoreValve devices in a single center: the Milan experience. *JACC Cardiovasc Interv* 2010;**3**:1110–1121.
20. Godin M, Eltchaninoff H, Furuta A, Tron C, Anselme F, Bejar K, Sanchez-Giron C, Bauer F, Litzler P, Bessou J, Cribier A. Frequency of conduction disturbances after transcatheter implantation of an Edwards Sapien aortic valve prosthesis. *Am J Cardiol* 2010;**106**:707–712.
21. Calvi V, Puzzangara E, Pruiti G, Conti S, Di Grazia A, Ussia G, Capodanno D, Tamburino C. Early conduction disorders following percutaneous aortic valve replacement. *Pacing Clin Electrophysiol* 2009;**32** (Suppl 1):S126–S130.
22. Latsios G, Gerckens U, Buellesfeld L, Mueller R, John D, Yuecel S, Syring J, Sauren B, Grube E. Device landing zone calcification, assessed by MSCT, as a predictive factor for pacemaker implantation after TAVI. *Catheter Cardiovasc Interv* 2010;**76**:431–439.
23. McKay R, Safian R, Lock J, Diver D, Berman A, Warren S, Come P, Baim D, Mandell V, Royal H. Assessment of left ventricular and aortic valve function after aortic balloon valvuloplasty in adult patients with critical aortic stenosis. *Circulation* 1987;**75**:192–203.
24. Plack R, Porterfield J, Brinker J. Complete heart block developing during aortic valvuloplasty. *Chest* 1989;**96**:1201–1203.
25. Carlson M, Palacios I, Thomas J, Rottman J, Freeman C, Block P, Ruskin J, Garan H. Cardiac conduction abnormalities during percutaneous balloon mitral or aortic valvotomy. *Circulation* 1989;**79**:1197–1203.
26. Dawkins S, Hobson A, Kalra P, Tang A, Monro J, Dawkins K. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. *Ann Thorac Surg* 2008;**85**:108–112.
27. Limongelli G, Ducceschi V, D'Andrea A, Renzulli A, Sarubbi B, De Feo M, Cerasuolo F, Calabrò R, Cotrufo M. Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. *Heart* 2003;**89**:901–904.

28. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, Ramondo A, Ussia GP, Ettori F, Poli A, Brambilla N, Saia F, De Marco F, Colombo A. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv* 2010;**3**:359–366.
29. Bapat V, Thomas M, Hancock J, Wilson K. First successful trans-catheter aortic valve implantation through ascending aorta using Edwards SAPIEN THV system. *Eur J Cardiothorac Surg* 2010;**38**:811–813.
30. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly 'no-access option' patients. *Catheter Cardiovasc Interv* 2010;**75**:1129–1136.
31. Lefèvre T, Kappetein AP, Wolner E, Nataf P, Thomas M, Schächinger V, De Bruyne B, Eltchaninoff H, Thielmann M, Himbert D, Romano M, Serruys P, Wimmer-Greinecker G, Group obotPEI. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. *Eur Heart J* 2011;**32**:148–157.
32. Treede H, Tübler T, Reichenspurner H, Grube E, Pascotto A, Franzen O, Mueller R, Low R, Bolling SF, Meinertz T, Schofer J. Six-month results of a repositionable and retrievable pericardial valve for transcatheter aortic valve replacement: the Direct Flow Medical aortic valve. *J Thorac Cardiovasc Surg* 2010;**140**:897–903.

CHAPTER 6

Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation

Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation

Nicolo Piazza[1], MD; Rutger-Jan Nuis[1], MD; Apostolos Tzikas[1], MD; Amber Otten[1], MD; Yoshinobu Onuma[1], MD; Hector Garcia Garcia[1], MD; Carl Schultz[1], MD; Ron van Domburg[2], PhD; Gerrit-Anne van Es[3], PhD; Robert van Geuns[1], MD; Peter de Jaegere[1], MD; Patrick W. Serruys[1]*, MD, PhD

1. Interventional Cardiology, Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands; 2. Department of Epidemiology and Biostatistics, Erasmus Medical Center, Thoraxcenter, Rotterdam, The Netherlands; 3. Department of Biostatistics, Cardialysis, Rotterdam, The Netherlands

N. Piazza is a consultant to Medtronic. P. de Jaegere is a proctor for Medtronic. G.van Es is an employee of Cardialysis. The other authors have no conflicts of interest to declare.

KEYWORDS

TAVI, conduction abnormalities, pacemaking

Abstract

Aims: Early conduction abnormalities and need for pacemaking after transcatheter aortic valve implantation (TAVI) is well recognised. It is still unknown, however, if these conduction abnormalities are persistent, and what is the need for permanent pacemaking after 1-month follow-up. In this prospective study, we examined the incidence of post-procedural and 6-month conduction abnormalities and need for permanent pacemaking after TAVI.

Methods and results: We examined the 12-lead electrocardiogram (ECG) of 91 consecutive patients in whom a Medtronic CoreValve ReValving System was implanted between November 2005 and April 2009. We evaluated the ECGs before treatment, after treatment, at 1-month and 6-month follow-up. The requirement and timing of permanent pacemaking was documented. The mean age of patients was 81±7 years and the mean logistic EuroSCORE was 16±9%. Median duration of follow-up was 213 days (IQR 64, 519). There was a 39% increase in the frequency of LBBB after TAVI (15% before treatment vs. 54% after treatment, p<0.001). Importantly, there was no significant change in the frequency of LBBB from after treatment to 1- or 6-month follow-up (54% after treatment vs. 42% at 1-month follow-up, p=0.45, and 54% after treatment vs. 45% at 6-month follow-up, p=0.39). Permanent pacemaking was required in 17/91 (19%) of patients. A permanent pacemaker was implanted in 8/17 patients (47%) within seven days of TAVI, in 6/17 (35%) at 7-30 days, and in 3/17 (18%) after 30 days. Male gender, previous myocardial infarction, pre-existing right bundle branch block, actual diameter (mm) of the inflow portion of the CoreValve frame post-implantation and depth of implantation were predictors for new LBBB; pre-treatment QRS duration (msec) and septal wall thickness were predictors for permanent pacemaking.

Conclusions: These results suggest that early conduction abnormalities occurring after TAVI persist at 6-months follow-up. Patient-related, anatomical-related, and procedure-related factors need to be considered in the pathogenesis of conduction abnormalities after TAVI.

** Corresponding author: Thoraxcenter, Ba583a, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands*
E-mail: p.w.j.c.serruys@erasmusmc.nl

Introduction

Early conduction abnormalities and need for pacemaking is well recognised after transcatheter aortic valve implantation (TAVI)[1-4]. The occurrence of conduction abnormalities is not surprising when one considers the anatomical proximity of the aortic valvar complex to the conduction system[5]. Furthermore, pre-existing conduction abnormalities are common in patients with aortic valvar stenosis[6,7].

In our previous work, we demonstrated a 40% increase in the occurrence of LBBB after TAVI[1]. Although there was a non-significant decrease in the frequency of LBBB from the time after implantation to 1-month follow-up, there was a significant decrease in QRS duration suggesting an improvement in intraventricular conduction. Furthermore, a correlation was found between the depth of implantation of the prosthesis within the left ventricular outflow tract and the occurrence left bundle branch block. Although the clinical implications of new LBBB acquired after TAVI are yet unknown, it is apparent from the surgical literature that new and persistent bundle branch block acquired after aortic valve replacement is associated with an increased risk of subsequent arrhythmic events, such as syncope, AV dissociation, and sudden death[8]. Furthermore, left bundle branch block can be associated with left ventricular mechanical dyssynchrony, left ventricular remodelling and impaired systolic and diastolic heart function[9].

It is still unknown, however, if conduction abnormalities occurring after TAVI are persistent, and what is the need for permanent pacemaking after 1-month follow-up. In this prospective study, we examined the incidence of conduction abnormalities up to 6-month follow-up and need for permanent pacemaking. Furthermore, we sought to identify predictors of left bundle branch block and need for permanent pacemaking acquired after TAVI.

Methods

Patients

We prospectively enrolled consecutive patients with severe aortic stenosis in whom a CoreValve ReValving System (Medtronic, Minneapolis, MN, USA) was implanted between November 2005 and April 2009. For a patient to undergo TAVI, a Heart Team (specifically an interventional cardiologist and cardiac surgeon) had to agree that surgical aortic valve replacement would be associated with either high or prohibitive risk.

Inclusion and exclusion criteria for implantation of the CoreValve ReValving System are in accordance with the 18 Fr Expanded Evaluation Registry study criteria and have been described elsewhere[10].

Description of the device and procedure

The CoreValve bioprosthesis consists of a self-expanding nitinol tri-level frame to which is sewn a trileaflet porcine pericardial heart valve. The non-cylindrical frame design exhibits three different diameters associated with three different degrees of radial stiffness. In particular, the (lower) inflow level of the frame exerts high radial stiffness for secure intra-annular anchoring. This inflow portion of the frame has been implicated in the development of conduction abnormalities depending on its depth of implantation[1].

The prosthesis is currently available in two sizes based on the diameter of its inflow portion (or ventricular end): 26 or 29 mm. Selection of the prosthesis size is dependent on measurements of the aortic root and ascending aorta[5].

Technical details of the procedure have been previously published[11]. Briefly, a temporary pacemaker was implanted via the femoral vein and positioned in the right ventricle at the beginning of the procedure. Balloon aortic valvuloplasty was performed in all patients before valve implantation. Positioning and deployment of the device was guided by fluoroscopic and angiographic imaging. During our initial experience, it was recommended to position the ventricular edge of the prosthesis 10-12 mm below the lower edge of the non-coronary leaflet. As a result of our previous work relating depth of implantation to the development of conduction abnormalities, we now intend to position the ventricular edge of the prosthesis approximately 6-7 mm below the lower edge of the non-coronary leaflet[1].

Following valve implantation, the temporary pacemaker was left in place for 24-72 hours and subsequently removed in the absence of high-degree atrioventricular block. Patients were further monitored by telemetry until discharge.

Collection of ECG and pacemaking data

Twelve-lead electrocardiographic recordings were obtained before treatment, after treatment, at 1-month and 6-month follow-up and examined by a core laboratory (Cardialysis, Rotterdam, The Netherlands). More specifically, the ECGs were analysed for rhythm, heart rate (beats/min), PR, QRS, and corrected QT intervals (all in milliseconds), and the presence of atrioventricular block (first, second, and third degree).

In addition, the diagnostic criteria endorsed by the World Health Organisation and International Society and Federation for Cardiology Task Force were used to code for right and left fascicular hemi block and right and left bundle branch block[12].

A continuous 3-lead rhythm strip was continuously recorded and stored electronically. We subsequently analysed the rhythm strips for new widening of the QRS duration (i.e., ≥120 msec) and further categorised the event as occurring either before or after valve implantation.

We documented the need for temporary or permanent pacemaking. Furthermore, the indication and timing of permanent pacemaker implantation from valve implantation (days) was recorded.

Quantitative angiographic measurements (depth of implantation of the frame, percent expansion of the inflow portion of the frame, aortic root angle)

Quantitative angiographic analysis was performed using CAAS 5.4 software (Pie Medical, Maastricht, The Netherlands). Calibration was achieved using a graduated pigtail with radiopaque markers separated 10 mm apart.

We measured the depth of implantation of the frame defined as the distance from the lower edge of the non-coronary and left coronary leaflet to the ventricular edge of the frame. We sought to correlate the depth of implantation of the frame to the occurrence of left bundle branch block acquired specifically after valve implantation (as opposed to new-onset left bundle branch block occurring before valve implantation) (Figure 1). As a result of our previous work

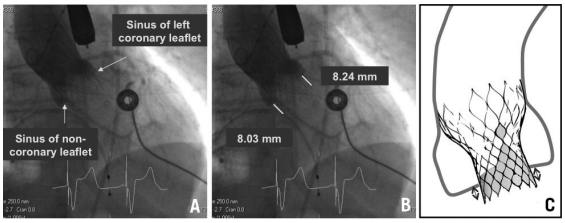


Figure 1. Measurement of depth of implantation from the base of the non-coronary and left coronary sinus to the ventricular end of the bioprosthesis. (A) Contrast aortography performed after CoreValve implantation. (B) Same figure as in A but includes measurements of the depth of implantation. (C) Pictorial diagram demonstrating depth of implantation (double-headed arrows).

relating depth of implantation to the development of conduction abnormalities, we now aim to position the ventricular edge of the prosthesis approximately 6-7 mm below the lower edge of the non-coronary leaflet. In an effort to assess the clinical impact of our previous findings[1], we also compared the first half and second half of patients with respect to the depth of implantation from the non-coronary sinus.

The percent expansion of the inflow portion of the frame was defined as the diameter of the inflow portion of the frame measured by quantitative techniques divided by the nominal diameter of the inflow portion of the frame (either 26 or 29 mm depending on the size of the valve implanted). This was calculated in two orthogonal views using biplane imaging. We wanted to investigate the association between the actual expansion of the inflow portion of the frame and newly acquired conduction abnormalities.

Statistical analysis

Continuous variables are presented as means (±SD) or median (interquartile range, IQR) depending if the data is normally or non-normally distributed, respectively. Categorical variables are presented as frequencies. The Wilcoxon signed-rank test (for continuous variable) and the McNemar test conducted by exact methods (for binomial variables) were used to perform paired comparisons between pre-treatment vs. after treatment, pre-treatment vs. 1-month follow-up, pre-treatment vs. 6-month follow-up, after treatment vs. 1-month follow-up, after treatment vs. 6-month follow-up, and 1-month vs. 6-month follow-up. The analysis was performed upon the entire cohort that included 89 available ECGs before treatment, 85 after treatment, 47 at 1-month follow-up, and 45 at 6-month follow-up. To verify the consistency of the results, the analysis was repeated upon a cohort of 44 patients who had complete serial ECG follow-up.

We used a univariable logistic regression model to examine for separate predictors of new-onset left bundle branch block acquired after valve implantation (as opposed to new-onset left bundle branch block acquired before the valve was implanted) or new permanent pacemaking. Patients with pre-existing LBBB or pre-existing permanent pacemakers were excluded from the respective analyses. The following variables were included in the univariable analysis: baseline characteristics listed in Table 1, conduction abnormalities identified on the baseline ECG interpreted from Table 2, septal wall thickness (mm), the size of implanted valve (26 or 29 mm), ratio of the size of implanted valve to the diameter of the aortic valve annulus, diameter of the inflow portion of the frame (in AP and lateral projections), depth of implantation of the frame (from the non-coronary and left coronary view) and post-implant dilatation.

Statistical tests were two-sided with a p-value of < 0.05 indicating statistical significance. All statistical analyses were performed with SPSS software version 12 (SPSS Institute, Chicago, IL, USA).

Table 1. Baseline characteristics

	n=91
Age, yrs. (mean±SD)	81±7
Male, n (%)	39 (43)
Coronary artery disease, n (%)	48 (53)
History of myocardial infarction	20 (23)
History of percutaneous coronary intervention, n (%)	20 (22)
History of coronary artery bypass, n (%)	26 (29)
Left ventricular ejection fraction, % (mean ± SD)	52±14.7
Permanent pacemaker, n (%)	8 (9)
Diabetes, n (%)	18 (20)
Hypertension, n (%)	46 (51)
Chronic renal failure, n (%)	82 (93)
Aortic valve area (cm^2), mean±SD	0.62±0.19
LVOT diameter (mm), mean±SD	19.3±2.63
Mitral annular calcification, n (%)	27 (31)
Prosthesis inflow size, n (%)	
26-mm	42 (47)
29-mm	47 (53)

Results

We prospectively enrolled 91 consecutive patients in whom a CoreValve ReValving System was implanted between November 2005 and April 2009. Baseline characteristics are listed in Table 1. As a result of three intra-procedural deaths, procedural success was achieved in 88/91 patients (97%). Median duration of follow-up was 213 days (IQR 64, 519). Cumulative survival at 30 days and six months was 87% and 83%, respectively. Survival data was 100% complete at 1- and 6-month follow-up.

At 6-month follow-up, 28/91 patients (31%) had died. Sudden cardiac death (SCD) was responsible for 5/28 deaths (18%); these occurred on day 8, 244, 282, 400 and 887. In these patients, the latest electrocardiographic findings demonstrated normal sinus rhythm in one, incomplete left bundle branch block in one, left bundle branch in two, and a paced rhythm in one patient.

Twelve-lead ECG evaluation

The number of 12-lead ECGs analysed at each follow-up interval is shown in Figure 2. Results of the ECG interpretation are shown in Table 2 for the total cohort.

RHYTHM

The percent of patients in sinus rhythm decreased significantly from 70% before treatment to 55% after treatment (p=0.002). This decrease remained significant at 1- and 6-month follow-up (70 vs. 44%, p < 0.001 and 70 vs. 58%, p=0.021, respectively).

There was a significant increase in the frequency of paced rhythm after device insertion (2% before vs. 16% after treatment, p <0.001) that was maintained at 1- and 6-month follow-up (2% before vs. 21% at 1-month follow-up, p=0.004, and 2% before vs. 18% at 6-month follow-up, p=0.031).

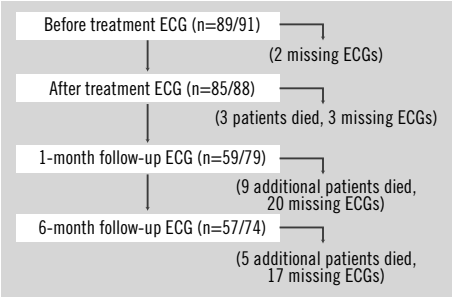


Figure 2. Patient flow diagram showing number of 12-lead electrocardiograms (ECGs) available for interpretation.

QRS DURATION

After device insertion, there was a significant increase in QRS duration (110±26 before treatment vs. 141±31 msec after treatment, p <0.001). Although the QRS duration decreased significantly from after treatment to 1- and 6-month follow-up (141±31 after treatment vs. 131±29 msec at 1-month follow-up, p <0.001 and 141±31 after treatment vs. 134±30 msec at 6-month follow-up, p < 0.001, respectively), there was no significant change between 1 and 6-month follow-up (131±29 at 1-month follow-up vs. 134±30 msec at 6-month follow-up, p=0.79).

Analysis of individual patient data from 1- to 6-month follow-up demonstrated that 45% had a decrease in QRS width, 19% had no change, and 36% had an increase. The range for the differences in QRS width from 1- to 6-month follow-up was –52 to 58 msec.

BUNDLE BRANCH BLOCK

New-onset left bundle branch block (LBBB) occurred in 38% of patients after device insertion (15% before treatment vs. 53% after treatment, p <0.001). The number of patients with new-onset LBBB remained significantly higher at 1- and 6-month follow-up than at baseline (15% before treatment vs. 44% at 1-month follow-up, p=0.004, and 15% before treatment vs. 43% at 6-month follow-up, p=0.001, respectively). Furthermore, there was no significant change in the frequency of LBBB from after treatment to 1- or 6-

Table 2. Interpretation of electrocardiograms before treatment after treatment 1-month follow-up and 6-month follow-up (overall cohort).

	Before treatement (n=89)	After treatment (n=85)	1 month (n=59)	6 month (n=57)	p Value before treatment vs. after treatment	p Value before treatment vs. 1-month follow-up	p Value before treatment vs. 6-month follow-up	p Value after treatment vs. 1-month follow-up	p Value after treatment vs. 6-month follow-up
Rhythm, n (%)									
Sinus	62(70)	48(55)	27(46)	33(58)	0.002	<0.001	0.021	0.289	1.000
Atrial fibrillation	25(28)	23(26)	20(34)	14(25)	1.000	0.687	1.000	0.453	1.000
Pacemaker	2(2)	14(16)	12(20)	10(18)	<0.001	0.001	0.008	0.625	0.727
Junctional	0(0)	2(2)	0(0)	0(0)	0.500	0.500	0.500		1.000
Heart rate (bpm)	73±13	77±19	78±13	76±17	0.029	0.102	0.077	0.570	0.960
PR interval (msec)	186±33	184±36	180±32	181±50	0.744	0.976	0.656	0.715	0.280
QRS width (msec)	110±26	141±31	133±35	135±31	<0.001	<0.001	<0.001	<0.001	<0.001
QT interval (msec)	427±39	469±45	437±38	436±34	<0.001	0.015	0.001	<0.001	<0.001
Hemiblock, n (%)									
None	74(83)	82(99)	54(95)	53(93)	0.002	0.109	0.180	0.500	0.375
Anterior	13(15)	1(1)	3(5)	4(7)	0.006	0.289	0.219	0.500	0.375
Posterior	2(2)	0(0)	0(0)	0(0)	1.000	0.500	1.000	1.000	1.000
Bundle branch block, n (%)									
None	66(74)	26(31)	27(47)	25(45)	<0.001	0.027	0.210	0.006	0.003
Left	13(15)	45(54)	24(42)	25(45)	<0.001	0.001	<0.001	0.453	0.388
Right	5(6)	4(5)	2(4)	1(2)	1.000	1.000	0.500	0.500	0.375
Incomplete left	4(5)	8(10)	4(7)	4(7)	0.344	1.000	1.000	0.625	1.000
Incomplete right	1(1)	0(0)	0(0)	1(2)	1.000	1.000	1.000	1.000	1.000

month follow-up (53% after treatment vs. 44% at 1-month follow-up, p=1.0, and 53% after treatment vs. 43% at 1-month follow-up, p=0.45).

SERIAL ECG FOLLOW-UP IN 44 PATIENTS

Similar results to those of the entire cohort (Table 2) were observed in 44 patients with complete serial ECG follow-up (Table 3).

TIMING OF QRS WIDENING

Examination of the intra-procedural 3-lead rhythm strip revealed that QRS widening occurred before and after valve implantation in 48% and 52% of patients, respectively. In those cases occurring before valve implantation, there was a temporal relation with either wire crossing of the native aortic valve or pre-implantation balloon aortic valvuloplasty.

NEED FOR PACEMAKING

Approximately one-tenth of patients had a history permanent pacemaker implantation before valve insertion (Table 1). During the procedure, the need for temporary pacemaking was documented in 19/91 patients (21%). Of those with a requirement for temporary pacemaking, 13/19 patients (68%) ultimately received a permanent pacemaker.

There were 17 patients who ultimately received a new permanent pacemaker. Considering the fact that there were three intra-procedural deaths and eight patients with a prior history of permanent pacemaker, 17/80 patients (21%) had a requirement for new permanent pacemaking. Thus, 13/17 patients (76%) implanted with a permanent pacemaker had a documentation of temporary pacemaking during the procedure. Third degree atrioventricular block was the indication for permanent pacemaker implantation in 14/17 patients (82%). The permanent pacemaker was implanted within seven days of the index procedure in 8/17 patients (47%), within 7-30 days in 6/17 patients (35%), and after 30 days in 3/17 (18%) (Table 4). More precisely, the median time from valve to permanent pacemaker implantation was seven days (IQR 6, 18 days). Furthermore, the vast majority of patients (88%) had the permanent pacemaker implanted during their hospitalisation. The median length of hospital stay was significantly longer in patients implanted with a new permanent pacemaker than in those not implanted with a permanent pacemaker (17 IQR 9, 21 days vs. 9 IQR 7, 12 days, p=0.015).

All five patients with a pre-existing right bundle branch block developed complete heart block after device insertion.

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS

Measurements of the depth of implantation of the frame (mm) and diameter of the inflow portion of the frame (percent expansion and difference between nominal (26 or 29 mm inflow) and actual measurements) are shown in Table 5. The depth of implantation measured from the non-coronary sinus was significantly greater in patients who developed LBBB after the valve was implanted than in those who did not develop LBBB or did develop LBBB but before the valve was implanted (7.3±2.7 vs. 10.2±2.6 mm, p<0.001); there was no difference in depth of implantation relative to the left coronary sinus (8.6±3.8 vs. 10.4±4.0 mm, p=0.106). Figure 3 shows the positive correlation between the depth of implantation and percent expansion of the inflow portion of the frame and its relationship to the development of LBBB after valve implantation. Despite our intention to implant the valve at a target depth of 6-7 mm, we did not find a significant difference in the depth of implantation between the first- and second-half of the study patients (8.2±2.9 mm vs. 7.8±2.9 mm, respectively, p=0.56).

Table 3. Interpretation of electrocardiograms before treatment after treatment at 1-month follow-up and 6-month follow-up (serial cohort of 44 patients).

	Before treatement (n=44)	After treatment (n=44)	1 month (n=44)	6 month (n=44)	p Value before treatment vs. after treatment	p Value before treatment vs. 1-month follow-up	p Value before treatment vs. 6-month follow-up	p Value after treatment vs. 1-month follow-up	p Value after treatment vs. 6-month follow-up
Rhythm, n (%)									
Sinus	30(70)	24(55)	23(52)	24(55)	0.039	0.008	0.070	1.000	1.000
Atrial fibrillation	12(28)	12(37)	14(32)	13(30)	1.000	0.625	1.000	0.625	1.000
Pacemaker	1(2)	6(14)	7(16)	7(16)	0.063	0.031	0.063	1.000	1.000
Junctional	0(0)	2(5)	0(0)	0(0)	0.500	0.500	1.000	0.500	0.500
Heart rate (bpm)	74±12	76±16	77±13	78±18	0.041	0.005	0.088	0.259	0.500
PR Interval (msec)	180±26	176±36	179±33	170±45	0.887	0.798	0.343	0.826	0.793
QRS width (msec)	110±26	14229	133±29	132±32	<0.001	0.001	<0.001	0.002	0.889
QT interval (msec)	422±32	461±42	437±34	435±31	<0.001	0.003	0.011	0.014	0.025
Hemiblock, n(%)									
None	36(84)	42(96)	41(93)	41(93)	0.070	0.289	0.289	0.500	0.625
Anterior	6(14)	1(2)	3(7)	3(7)	0.125	0.453	0.375	0.500	0.625
Posterior	1(2)	1(2)	0(0)	0(0)	1.000	1.000	1.000	1.000	1.000
Bundle branch block, n(%)									
None	29(67)	13(30)	18(41)	20(47)	0.001	0.031	0.648	0.070	0.001
Left	7(16)	21(48)	21(48)	19(44)	0.002	0.001	0.001	1.000	1.000
Right	2(5)	4(9)	2(5)	0(0)	0.625	1.000	0.500	0.500	0.125
Incomplete left	4(9)	6(14)	3(7)	3(7)	0.727	1.000	1.000	0.250	0.687
Incomplete right	1(2)	0(0)	0(0)	1(2)	1.000	1.000	1.000	1.000	1.000

Table 4. Permanent pacemaking requirements after TAVI.

Patient number	Baseline ECG	Temporary PM	Permanent PM	Permanent pacemaker implanted during index hospitalisation or post-discharge	Days after TAVI Permanent PM implanted	Indication for Permanent PM	Timing when AVB noticed
<7 Days, n=8							
14	SR. LAFB	No	VVI	Index hospitalisation	4	3rd degree AVB	Post procedural
24	SR. LBBB	Yes	DDDR	Index hospitalisation	6	3rd deqree AVB	Intra procedural
30	SR. RBBB	Yes	DDDICD	Index hospitalisation	6	3rd deqree AVB	Intra procedural
33	SR. NC	Yes	DDDR	Index hospitalisation	6	3rd degree AVB	Infra procedural
47	SR. RBBB	Yes	DDDR	Index hospitalisation	6	3rd degree AVB	Intra procedural
69	SR. RBBB	Yes	DDDR	Index hospitalisation	2	3rd degree AVB	Intra procedural
73	SR. RBBB	Yes	DDDR	Index hospitalisation	6	3rd degree AVB	Intra procedural
75	SR. NC	Yes	DDDR	Index hospitalisation	1	3rd degree AVB	Intra procecural
7-30 Days, n=6							
8	SR. NC	No	VVI	Index hospitalisation	18	2nd degree AVB*	Post procedural
54	AF. NC	Yes	VVI	Index hospitalisation	7	3rd degree AVB	Post procedural
66	AF. NC	Yes	VVI	Index hospitalisation	9	3rd degree AVB	Intra procedural
71	SR. NC	Yes	DDDR	Index hospitalisation	7	3rd degree AVB	Intra procedural
81	AF. LBBB	Yes	VVI	Index hospitalisation	14	3rd deqree AVB	Intra procedural
91	SR. NC	Yes	DDDR	Index hospitalisation	18	3rd degree AVB	Intra procedural
>30 Days, n=3							
4	SR. NC	Yes	DDDICD	Post-discharqe	41	3rd degree AVB	Post procedural
9	SR. NC	No	DDDICD	Index hospitalisation	46	Bradyarrhythmia/NSVT	Post procedural
18	SR. NC	No	DDDR	Post-discharge	423	Syncope	Post procedural

AF: atrial fibrillation; AVB: atrioventricular block; LAFB: left anterior fascicular block; LBBB: left bundle branch block; NC: normal conduction; NSVT: non-sustained ventricular tachycardia; PM: pacemaker; RBBB: right bundle branch; *Type II

Table 5. Quantitative angiographic measurements.

	Mean±SD
Overall cohort (n=91)	
Depth of implantation - left coronary leaflet, mm (±SD)	9.1 (±3.4)
Depth of implantation - noncoronary leaflet, mm (±SD)	8.0 (±2.5)
New-onset LBBB acquired during or after valve implantation	
Depth of implantation - left coronary leaflet, mm (±SD)	10.4 (±4.0)
Depth of implantation - noncoronary leaflet, mm (±SD)	10.2 (±2.6)
No new-onset LBBB or new-onset LBBB acquired during procedure but before valve implantation	
Depth of implantation - left coronary leaflet, mm (±SD)	8.6 (±3.8)
Depth of implantation - noncoronary leaflet, mm (±SD)	7.3 (±2.7)
Percent expansion of inflow portion of frame - AP view, % (±SD)	83 (±10)
Percent expansion of inflow portion of frame - Lateral view, % (±SD)	78 (±10)

PREDICTORS OF NEW-ONSET LEFT BUNDLE BRANCH BLOCK AND NEED FOR PERMANENT PACEMAKING

Tables 6 and 7 show the results of the univariable analysis for predictors of new-onset LBBB and need for new permanent pacemaking, respectively.

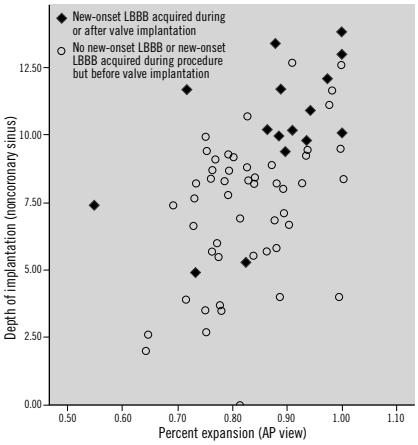


Figure 3. Correlation between depth of implantation (from the non-coronary sinus) and percent expansion of inflow level of the CoreValve (relative to valve size 26- or 29-mm). Pearson Correlation Coefficient 0.51, p<0.001.

Discussion

In this study we found that early conduction abnormalities (LBBB) occurring after CoreValve implantation persisted at 6-month follow-up. In addition, one-fifth of patients had implantation of a new permanent pacemaker –50% were implanted seven days after the TAVI procedure. Predictors of new-onset LBBB were male gender, previous history of myocardial infarction, pre-existing right bundle branch block, actual diameter of the inflow portion of the frame after implantation and depth of implantation. Predictors for new permanent pacemaking were pre-treatment QRS duration (msec) and septal wall thickness. Finally, we propose a framework to understand the potential mechanisms implicated in the development of conduction abnormalities after TAVI.

Table 6. Univariable analysis for predictors of new-onset LBBB after valve implantation.

	OR (95% CI)	P value
Baseline patient characteristics		
Age (years)	1.04 (0.92 to 1.10)	0.93
Gender	3.96 (1.12 to 14.06)	0.033
Logistic EuroSCORE (%)	1.00 (0.94 to 1.07)	1.00
New York Heart Association (I-IV)		
II	Reference	0.41
III	0	1.00
IV	4.33 (0.51 to 36.70)	0.18
Hypertension	3.24 (0.92 to 11.47)	0.068
Diabetes mellitus	1.67 (0.45 to 6.24)	0.45
Coronary artery disease	1.33 (0.41 to 4.30)	0.63
Myocardial infarction	3.48 (1.00 to 12.05)	0.049
Percutaneous coronary intervention	1.67 (0.45 to 6.24)	0.45
Coronary artery bypass graft surgery	0.96 (0.27 to 3.53)	0.97
History of atrial fibrillation	1.01 (0.24 to 4.15)	0.99
Stroke	1.37 (0.37 to 5.05)	0.64
Peripheral vascular disease	5.00 (0.64 to 39.06)	0.13
Chronic renal failure	1.45 (0.30 to 6.92)	0.64
Dialysis	0.67 (0.35 to 1.29)	0.23
Chronic obstructive pulmonary disease	1.06 (0.29 to 3.83)	0.93
Pulmonary hypertension	1.36 (0.42 to 4.44)	0.61
Baseline echocardiography		
Left ventricular outflow tract (mm)	1.13 (0.89 to 1.43)	0.33
Aortic valve annulus (mm)	0.974 (0.71 to 1.23)	0.63
Septal wall thickness (mm)	0.83 (0.65 to 1.07)	0.16
Aortic valve area (cm^2)	0.73 (0.03 to 17.52)	0.84
Ejection fraction (%)	0.98 (0.94 to 1.03)	0.40
Mitral annular calcification	0.48 (0.12 to 1.92)	0.30
Baseline electrocardiogram		
Cardiac rhythm		
Sinus	Reference	0.64
Atrial fibrillation	1.83 (0.53 to 6.35)	0.34
PR interval (msec)	1.00 (0.98 to 1.02)	0.91
QRS duration (msec)	0.99 (0.96 to 1.02)	0.48
QT interval (msec)	1.00 (0.98 to 1.01)	0.78
Hemiblock		
None	Reference	0.92
Left anterior hemiblock	1.36 (0.32 to 5.79)	0.67
Left posterior hemiblock	0	1.00
Bundle branch block		
No bundle branch block	Reference	0.17
RBBB	15.00 (1.43 to 157.90)	0.024
Procedural-related factors		
Valve size		
26 mm inflow	Reference	1.00
29 mm inflow	1.87 (0.58 to 6.05)	0.30
Measurement of inflow diameter (mm) - AP view	1.27 (1.01 to 1.61)	0.046
Measurement of inflow diameter (mm) - Lateral	1.26 (0.9 to 1.65)	0.083
Ratio of valve size (26- or 29-mm) to AV annulus (mm)	9.63 (0.38 to 246.46)	0.17
Depth of implantation from non-coronary leaflet (mm)	1.20 (1.32 to 3.17)	0.001
Depth of implantation from left coronary leaflet (mm)	1.20 (1.01 to 1.43)	0.037
Post-implant dilatation	1.71 (0.35 to 8.37)	0.51

Table 7. Univariable analysis for predictors of new permanent pacemaking.

	OR (95% CI)	P value
Baseline patient characteristics		
Age (years)	1.02 (0.94 to 1.12)	0.59
Gender	1.58 (0.53 to 4.72)	0.42
Logistic EuroSCORE (%)	1.01 (0.96 to 1.07)	0.67
New York Head Association (I-IV)		
II	Reference	0.89
III	0.73 (0.17 to 3.12)	0.67
IV	0.91 (0.15 to 5.58)	0.92
Hypertension	1.25 (0.42 to 3.74)	0.69
Diabetes mellitus	1.53 (0.42 to 5.56)	0.52
Coronary artery disease	0.52 (0.17 to 1.58)	0.25
Myocardial infarction	0.50 (0.10 to 2.43)	0.39
Percutaneous coronary intervention	0.39 (0.08 to 1.88)	0.24
Coronary artery bypass graft surgery	1.45 (0.44 to 4.80)	0.54
History of atrial fibrillation	0.63 (0.16 to 2.46)	0.51
Stroke	0.42 (0.09 to 2.04)	0.28
Peripheral vascular disease	1.42 (0.14 to 14.65)	0.78
Chronic renal failure	3.54 (0.75 to 16.69)	0.11
Dialysis	1.05 (0.60 to 1.82)	0.88
Chronic obstructive pulmonary disease	0.36 (0.08 to 1.74)	0.20
Pulmonary hypertension	2.20 (0.72 to 6.63)	0.17
Baseline echocardiography		
Left ventricular outflow tract (mm)	1.13 (0.89 to 1.43)	0.33
Aortic valve annulus (mm)	0.974 (0.71 to 1.23)	0.63
Septal wall thickness (mm)	1.28 (1.03 to 1.60)	0.026
Aortic valve area (cm^2)	2.79 (0.13 to 59 13)	0.51
Ejection fraction (%)	1.00 (0.96 to 1.03)	0.70
Mitral annular calcification	0.72 (0.21 to 2.50)	0.60
Baseline electrocardiogram		
Cardiac rhythm		
Sinus	Reference	1.00
Atrial fibrillation	2.45 (0.50 to 11.88)	0.21
PR interval (msec)	1.01 (0.99 to 1.03)	0.39
QRS duration (msec)	1.03 (1.00 to 1.05)	0.020
QT interval (msec)	1.01 (1.00 to 1.03)	0.070
Hemiblock		
None	Reference	0.55
Left anterior hemiblock	0.22 (0.01 to 3.81)	0.30
Left posterior hemiblock	0.18 (0.01 to 4.26)	0.29
Bundle branch block		
No bundle branch block	Reference	0.55
LBBB	0.82(0.16 to 4.18)	0.81
RBBB	4.50(026 to 77.14)	0.30
Procedural-related factors		
Valve size		
26 mm inflow	Reference	1.0
29 mm inflow	1.50(0.50 to 4.51)	0.47
Measurement of inflow diameter (mm) - AP view	0.93 (0.76 to 1.13)	0.47
Measurement of inflow diameter (mm) - Lateral	0.95 (0.78 to 1.16)	0.61
Ratio of valve size (26- or 29-mm) to AV annulus (mm)	0.57 (0.02 to 15.36)	0.74
Depth of implantation from non-coronary leaflet (mm)	0.93(0.76 to 1.13)	0.46
Depth of implantation from left coronary leaflet (mm)	1.05 (0.89 to 1.22)	0.58
Post-implant dilatation	1.88 (0.38 to 9.20)	0.44

We have previously demonstrated that new-onset LBBB is the most common conduction abnormality after implantation of the CoreValve device and is persistent at 1-month follow-up[1]. These findings have been confirmed by subsequent studies[3,4]. In our previous study, however, the observed decrease in QRS duration at 1-month follow-up (150±32 msec after treatment vs. 134±29 msec at 1-month follow-up, p<0.001) would seem to imply an improvement in conduction[1]. This led us to question whether conduction abnormalities occurring after CoreValve implantation were transient or persistent? Possible explanations include inflammation, oedema,

ischaemia and/or mechanical stress with recovery of conduction. In the present study, we observed a significant decrease in QRS duration from after treatment to 1-month follow-up (143±31 vs. 132±30 msec, p=0.002) but there was no significant change in QRS duration or frequency of LBBB from 1-month to 6-month follow-up. In contrast, Gutiérrez et al observed a significant decrease in QRS duration (msec) and frequency of new-onset LBBB from post-treatment to 1-month follow-up after implantation of the balloon-expandable Edwards prosthesis (Edwards Lifesciences, Irvine, CA, USA) such that there was no significant difference between baseline and 1-month follow-up (LBBB pre-treatment 9% vs. post-treatment 27% vs. 1-month follow-up 13% and QRS duration pre-treatment 114 vs. post-treatment 129 vs. 1-month follow-up 118 msec). We speculate that differences in QRS duration and new-onset LBBB overtime between the self-expandable and balloon-expandable transcatheter aortic valve systems may be related to technical differences (e.g., depth of implantation) and physical design properties of the frame and/or stent (self-expanding nitinol vs. balloon expandable stainless steel).

The implications of persistent LBBB after TAVI are currently unknown. What is known, however, is that acquirement of new bundle branch block after surgical aortic valve replacement is associated with increased risk of subsequent arrhythmic events after 1-year follow-up (specifically, syncope, AV dissociation, and sudden death)[8,13]. Our study was underpowered to pursue a similar analysis. These surgical reports propose prophylactic pacemaker insertion in patients who develop bundle branch block after aortic valve replacement[8,13].

In our centre, we do not implant "prophylactic" permanent pacemakers (e.g., for new-onset LBBB). The concept of "prophylactic" permanent pacemaker stems from the surgical literature. In a study of 133 patients undergoing surgical aortic valve replacement, Thomas et al observed that 32% of patients developed new-onset LBBB. At 2.5 years mean follow-up, the cumulative survival was 24% lower in those who developed new onset LBBB than in those who did not develop LBBB (66% vs. 90%, p<0.001) (reference). In a similar study of 389 patients undergoing surgical aortic valve replacement, El-Khally et al observed that 16% of patients developed a new-onset bundle branch block. At a mean follow-up of 4.5 years, the composite endpoint of complete heart block, syncope, and sudden cardiac death was 16% higher in those patients who developed bundle branch block than in those who did not develop bundle branch block. Both investigators concluded that "prophylactic permanent pacemaker" should be considered in patients who develop bundle branch block after surgical aortic valve replacement.

A new permanent pacemaker was inserted in approximately one-fifth of our patients after CoreValve implantation. The higher rate of permanent pacemaker implantation reported by other centres (up to 33%) most likely reflects a combination of "prophylactic" pacemaker implantation for concerns of patient safety and administrative logistics[4,14]. In our study, 3rd AV block was present in four-fifths of patients who received a new permanent pacemaker. Although 15/17 patients (88%) underwent permanent pacemaker implantation during hospitalisation, 9/17 (52%) patients underwent implantation seven days after valve implantation. The duration of hospitalisation was significantly longer in those patients who required permanent pacemaking than in those who did not require permanent pacemaking. Strategies to avoid unnecessary and prolonged hospitalisation due to pacemaker implantation should be the focus of future studies. Considering the fact that three-quarter of patients requiring temporary pacemaking ultimately required permanent pacemaking, immediate implantation of a permanent pacemaker in these particular patients may promote earlier mobilisation and discharge. In fact, anecdotal experiences seem to suggest that "prophylactic" permanent pacemaker implantation may conceivably lead to reduced hospital stay.

In the present study male gender, previous myocardial infarction, pre-existing right bundle branch block, diameter (mm) of the inflow portion of the frame after implantation, and depth of implantation were predictors for new-onset left bundle branch block.

Recently, Osamu et al examined the distance (mm) from the base of the non-coronary cusp to the lower edge of the membranous septum where the left bundle branch originated invariably in 100 autopsied hearts[15]. More specifically, the left bundle branch was located 6.3±2.4 mm from the base of the non-coronary cusp. Thus it is highly plausible that a deep implantation of the CoreValve device might play an important role in the occurrence of LBBB. The depth of the left bundle branch as noted by Osamu et al appears to be consistent with our suggestion to implant the CoreValve device <6-7 mm from the basal attachment of the aortic valve leaflets.

Two recent studies support our findings about the correlation between the depth of implantation and occurrence of LBBB after transcatheter aortic valve implantation. Gutiérrez et al observed a correlation between the depth of implantation of the Edwards SAPIEN (Edwards Lifesciences) device and the occurrence of left bundle branch block16. More specifically, 35% of patients in whom the ventricular end of the prosthesis was located below the hinge point of the anterior mitral leaflet developed left bundle branch block compared with none of the patients in whom the ventricular end was implanted above the hinge point (identified by transesophageal echocardiography) (p=0.029). In another study, Koektuerk et al found a correlation between the depth of implantation (>8 mm) of the CoreValve device assessed by fluoroscopy and the need for permanent pacemaking[17].

Despite our intentions to implant the prosthesis at a target depth of 6-7 mm, we did not find a significant difference in the depth of implantation between the first and second half of the study patients. This observation may question the technical feasibility (whether device- or operated-related) to precisely implant the CoreValve at a particular location. It is possible the learning curve and iterations in device design will improve the accuracy of device implantation.

In the present study, pre-treatment QRS duration and septal wall thickness were univariate predictors for permanent pacemaking. This would imply that patients with pre-existing conduction disease would have a greater chance of receiving a permanent pacemaker after CoreValve implantation. A single-centre study by Jilaihawi et al also identified septal wall thickness, in addition to LBBB with left axis deviation and non-coronary cusp thickness >8 mm as predictors for permanent pacemaking after CoreValve implantation[4]. Independent

predictors for permanent pacemaking after surgical aortic valve replacement include age, pre-existing right and left bundle branch block, aortic regurgitation at baseline, multivalvar surgery, left atrial enlargement, left ventricular dysfunction, pulmonary hypertension, previous myocardial infarction, and post-operative electrolyte imbalances[18-21].

As can be appreciated from Table 4, there was a discrepancy between the timing "when the AV block was first noticed" and "when the permanent pacemaker was implanted". Retrospective analysis of the patient dossiers revealed that the disparity between recognising the AV block and implantation of the permanent pacemaker was mainly due to administrative logistics and in some patients, urinary tract infection or low-grade fever of unknown origin that eventually resolved. Of the 15 patients who had a permanent pacemaker implanted during the index hospitalisation, AV block was recognised during the procedure in 11 patients (73%) and post-procedure in four patients (27%).

We propose the following framework to better understand the potential mechanisms involved in the development of conduction abnormalities: (1) patient-related; (2) anatomical-related; and (3) procedural-related (e.g., device or operator-related). Thus, gender, previous myocardial infarction and pre-existing right bundle branch block can be considered as patient-related factors; variations in the location of the left bundle branch exit point as an anatomical-related factor; self-expanding characteristics and high radial force of the CoreValve frame as device-related; and control of the depth of implantation as operator-related.

Study limitations

The following limitations need to be addressed. This report represents a single centre experience and therefore the results may not be generalisable. The results of this study relate to only one type of prosthesis and the conclusions, therefore, may not be applicable to other transcatheter aortic valve bioprostheses. Furthermore, variables (e.g., degree of aortic valve calcification) potentially associated with development of conduction abnormalities after CoreValve implantation may have been omitted from the analysis. The modest number of patients included in the analysis may have been underpowered to identify additional predictors of new LBBB or need for permanent pacemaking.

Currently, there is no gold standard to measure the depth of implantation of transcatheter aortic valves. In this study, the depth of implantation was measured by quantitative angiographic measurements using the "working" gantry angle (i.e., implantation viewing angle). The possibility exists that the depth of implantation was systematically underestimated. The alternative of overestimating the depth of implantation is not possible. Nevertheless, it was in this "working" gantry angle that the operators estimated the depth of implantation during the procedure. Also of note is that there was minimal overlap in the depth of implantation between those with new-onset LBBB vs. those who did not develop LBBB (10±2 mm vs. 7±2 mm, respectively). Alternative imaging modalities such as MSCT or echocardiography were not used to assess the depth of implantation and may have provided additional information.

This study was not designed to systematically interrogate newly implanted pacemakers at 1- and/or 6-months. It is possible that complete AV conduction disturbances may disappear as a sign of healing after some days or weeks.

Practical clinical implications

Our results would suggest that implanting the CoreValve prosthesis in a more superior location within the left ventricular outflow tract (i.e., depth of implantation <6-7 mm) might mitigate the occurrence of LBBB. It is likely that a number of inter-relating factors such as patient characteristics, anatomic variations, operator technique, and device characteristics are playing a role in the development of conduction abnormalities after TAVI. The clinical consequences of new-onset LBBB or new permanent pacemaking after CoreValve implantation are currently unknown.

The significant inter-hospital variations in the frequency of new permanent pacemaker reported in the literature likely reflects variations in physician threshold, country-based healthcare norms, and reimbursement strategies. There is currently a lack of standardised guidelines for new permanent pacemaker implantation, duration of temporary pacemaking, and duration of monitoring (in-hospital or post-discharge) after TAVI. In our centre, we use the AHA/ACC guidelines on when to implant a permanent pacemaker after TAVI[22]. The temporary pacemaker wire is typically removed on day 2-3 post-procedure. Subsequently, patients are maintained on telemetry monitoring for the duration of hospitalisation. An ECG is obtained at 1-month, 6-month, and 12-month clinical follow-up.

References

1. Piazza N, Onuma Y, Jesserun E, Kint PP, Maugenest AM, Anderson RH, de Jaegere P, Serruys PW. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after after percutaneous replacement of the aortic valve. *J Am Coll Cardiol Intv* 2008;1:310-316.

2. Sinhal A AL, Pasupati S, Humphries KH, Allard M, Martin P, Cheung A, Ye J, Kerr C, Lichenstein SV, Webb JG. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *J Am Coll Cardiol Intv* 2008;1:305-309.

3. Calvi V, Puzzangara E, Pruiti GP, Conti S, Di Grazia A, Ussia GP, Capodanno D, Tamburino C. Early conduction disorders following percutaneous aortic valve replacement. *Pacing Clin Electrophysiol* 2009;32 Suppl 1:S126-130.

4. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng GA, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *American heart journal* 2009;157:860-866.

5. Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Intervent* 2008;1:74-81.

6. Dhingra RC, Amat-y-Leon F, Pietras RJ, Wyndham C, Deedwania PC, Wu D, Denes P, Rosen KM. Sites of conduction disease in aortic stenosis: significance of valve gradient and calcification. *Annals of internal medicine* 1977;87:275-280.

7. Friedman HS, Zaman Q, Haft JI, Melendez S. Assessment of atrioventricular conduction in aortic valve disease. *British heart journal* 1978;40:911-917.

8. El-Khally Z TB, Staniloae C, Theroux P, Dubuc M, Roy D, Guerra P, Macle L, Talajic M. Prognostic significance of newly acquired bundle branch block after aortic valve replacement. *Am J Cardiol* 2004;94:1008-1011.

9. van Dijk J, Dijkmans PA, Gotte MJ, Spreeuwenberg MD, Visser CA, Kamp O. Evaluation of global left ventricular function and mechanical dyssynchrony in patients with an asymptomatic left bundle branch block: areal-time 3D echocardiography study. *Eur J Echocardiogr* 2008;9:40-46.

10. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, Laborde JC, de Jaegere P, Serruys PW. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18F) CoreValve ReValving System - Results from the Multicenter, Expanded Evaluation Registry 1-year following CE mark approval. *EuroIntervention* 2008;4:242-249.

11. de Jaegere P, van Dijk L, Laborde JC, Sianos G, Ramos FJO, Lighart J, Kappetein AP, vander Ent M, Serruys PW. True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar XL and the TandemHeart. *EuroIntervention* 2007;2:500-505.

12. Willems JL, Robles de Medina EO, Bernard R, Coumel P, Fisch C, Krikler D, Mazur NA, Meijler FL, Mogensen L, Moret P, et al. Criteria for intraventricular conduction disturbances and pre-excitation. World Health Organizational/International Society and Federation for Cardiology Task Force Ad Hoc. *Journal of the American College of Cardiology* 1985;5:1261-1275.

13. Thomas JL, Dickstein RA, Parker FB, Jr., Potts JL, Poirier RA, Fruehan CT, Eich RH. Prognostic significance of the development of left bundle conduction defects following aortic valve replacement. *The Journal of thoracic and cardiovascular surgery* 1982;84:382-386.

14. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, Beucher H, Felderhoff T, Iversen S, Gerckens U. Progress and Current Status of Percutaneous Aortic Valve Replacement: Results of Three Device Generations of the CoreValve Revalving System. *Circ Cardiovasc Intervent* 2008;1:167-175.

15. Igawa O, Adachi M, Yano A, Miake J, Inoue Y, Ogura K, Kato M, Iitsuka K, Kondo T, Hisatome I. Anatomical information for catheter ablation concerning the relationship between the aortic non-coronary cusp and the His-bundle. *Circ J* 2009;257:73.

16. Gutierrez M, Rodes-Cabau J, Bagur R, Doyle D, DeLarochelliere R, Bergeron S, Lemieux J, Villeneuve J, Cote M, Bertrand OF, Poirier P, Clavel MA, Pibarot P, Dumont E. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *American heart journal* 2009;158:302-308.

17. Koektuerk B, Schaefer U, Bergmann M, Schewel D, Geidel S, Kuck K. Acquired Conduction Disturbances After Percutaneous Aortic Valve Replacement. *Circulation* 2009;120:S307.

18. Koplan BA, Stevenson WG, Epstein LM, Aranki SF, Maisel WH. Development and validation of a simple risk score to predict the need for permanent pacing after cardiac valve surgery. *Journal of the American College of Cardiology* 2003;41:795-801.

19. Elahi MM, Osman KA, Bhandari M, Dhannapuneni RR. Does the type of prosthesis influence the incidence of permanent pacemaker implantation following isolated aortic valve replacement. *The heart surgery forum* 2005;8:E396-400.

20. Dawkins S, Hobson AR, Kalra PR, Tang AT, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. *The Annals of thoracic surgery* 2008;85:108-112.

21. Limongelli G, Ducceschi V, D'Andrea A, Renzulli A, Sarubbi B, De Feo M, Cerasuolo F, Calabro R, Cotrufo M. Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. *Heart* (British Cardiac Society) 2003;89:901-904.

22. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Journal of the American College of Cardiology* 2008;51:e1-62.

CHAPTER 7

Frequency of conduction abnormalities after transcatheter aortic valve implantation with the Medtronic-CoreValve and the effect on left ventricular ejection fraction

Frequency of Conduction Abnormalities After Transcatheter Aortic Valve Implantation With the Medtronic-CoreValve and the Effect on Left Ventricular Ejection Fraction

Apostolos Tzikas, MD*, Bas M. van Dalen, MD, PhD, Nicolas M. Van Mieghem, MD, Juan-Luis Gutierrez-Chico, MD, PhD, Rutger-Jan Nuis, MS, Floris Kauer, MD, Carl Schultz, MD, PhD, Patrick W. Serruys, MD, PhD, Peter P. T. de Jaegere, MD, PhD, and Marcel L. Geleijnse, MD, PhD

New conduction abnormalities occur frequently after transcatheter aortic valve implantation (TAVI). The relation between new conduction disorders and left ventricular (LV) systolic function after TAVI is unknown. The purpose of the present prospective, single-center study was to investigate the effect of TAVI on LV systolic function in relation to TAVI-induced conduction abnormalities. A total of 27 patients had undergone electrocardiography and transthoracic echocardiography the day before and 6 days after TAVI with the Medtronic-CoreValve system. The LV ejection fraction (EF) was calculated using the biplane Simpson method. The systolic mitral annular velocities and longitudinal strain were measured using speckle tracking echocardiography. After TAVI, 18 patients (67%) had new conduction abnormalities; 4 (15%) had a new paced rhythm and 14 patients (52%) had new left bundle branch block. In the patients with new conduction abnormalities, the EF decreased from 47 ± 12% to 44 ± 10%. In contrast, in those without new conduction abnormalities, the EF increased from 49 ± 12% to 54% ± 12%. The change in EF was significantly different among those with and without new conduction abnormalities ($p < 0.05$). In patients without new conduction abnormalities, an improvement was found in the systolic mitral annular velocities and longitudinal strain ($p < 0.05$). In contrast, in patients with new conduction abnormalities, the changes were not significant. In conclusion, the induction of new conduction abnormalities after TAVI with the Medtronic-CoreValve was associated with a lack of improvement in LV systolic function. **(Am J Cardiol 2011;107:285–289)**

Transcatheter aortic valve implantation (TAVI) is a new promising therapeutic option for high-risk patients with severe aortic stenosis.[1–5] The most experience has been achieved with the Medtronic-CoreValve system (Medtronic-CoreValve, Minneapolis, Minnesota) and the Edwards SAPIEN (Edwards Lifesiences, Irvine, California) bioprosthetic valve. Both devices have demonstrated favorable hemodynamic results, with a significant decrease in transaortic gradients and considerable clinical improvement. Despite this immediate decrease in the transaortic gradient, the left ventricular (LV) ejection fraction (EF) has been reported to remain unchanged after TAVI with the Medtronic-CoreValve.[6,7] More subtle measurements of LV systolic function have included mitral annular velocities and longitudinal strain (active deformation of the cardiac muscle). Speckle tracking echocardiography (STE) can assess both parameters reliably, independent of the angulation of the transducer and with optimal reproducibility.[8] After TAVI with the Medtronic-CoreValve, a left bundle branch block (LBBB) or an atrioventricular block requiring permanent pacemaker implantation occur in 40% to 65% and 20% to 33% of patients, respectively.[9–12] To date, the relation between the occurrence of conduction disorders and LV systolic function after TAVI is unknown. The purpose of the present prospective, single-center study was to investigate the effect of TAVI on LV systolic function in relation to TAVI-induced conduction abnormalities.

Methods

The study population included 27 consecutive patients who had undergone TAVI with the Medtronic-CoreValve and had transthoracic echocardiograms of adequate quality available before and after the procedure. The inclusion and exclusion criteria for TAVI have been previously described in detail.[3] In brief, the patients were included if they had severe native aortic valve stenosis with an aortic valve area <1 cm^2 or <0.6 cm^2/m^2, with or without aortic regurgitation, and were deemed high-risk surgical candidates. All patients provided written informed consent (postmarketing surveillance registry). The Medtronic-CoreValve System

Department of Cardiology, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received July 21, 2010; manuscript received and accepted September 14, 2010.

Dr Tzikas was supported by an unrestricted research grant from the European Association of Percutaneous Cardiovascular Interventions, Sophia Antipolis, France (EAPCI Interventional Cardiology Research Grant 2009).

*Corresponding author: Tel: (+31) 10-703-5656; fax: (+31) 10-703-4320.

E-mail address: aptzikas@yahoo.com (A. Tzikas).

consisted of a trileaflet porcine pericardial tissue valve, mounted in an hourglass-shaped, self-expanding nitinol frame (50 to 51 mm high). Currently, the prosthesis is available in sizes with a 26- and 29-mm inflow diameter for patient annulus diameters of 20 to 27 mm.

We obtained 12-lead electrocardiographic tracings in all patients before and after treatment and analyzed them for rhythm, heart rate, PR interval duration, QRS duration and morphology, and the presence of atrioventricular/fascicular block, according to recent recommendations.[13] In addition, an electronic single-lead rhythm strip was continuously recorded during the echocardiographic studies. The patients were considered to have new conduction abnormalities when a new LBBB or a new paced rhythm was recorded after the index procedure. The decision to implant a permanent pacemaker was determined according to the latest guidelines.[14]

Two-dimensional transthoracic echocardiography was performed by an independent experienced echocardiographer the day before and 1 week after the procedure, using a commercially available system (iE33, Philips, Best, The Netherlands) with the patient in the left lateral decubitus position, according to published recommendations.[15] All echocardiograms were saved as video loops or still frames in a digital database and were analyzed by a second independent investigator. The LVEF was calculated using the biplane modified Simpson rule. The transaortic peak velocity, peak and mean gradient, and velocity-time integral were measured using continuous-wave Doppler through the native or prosthetic aortic valve. The aortic valve area was estimated using the continuity equation approach [aortic valve area = LV outflow tract area × (velocity-time integral LV outflow tract/velocity-time integral valve)]. Aortic regurgitation and mitral regurgitation were assessed semiquantitatively according to the current guidelines for the evaluation of native valves.[16]

STE was performed using 2-dimensional grayscale harmonic images at a frame rate of 70 to 80 frames/s. The data sets were transferred to a QLAB workstation for analysis using the QLAB Advanced Quantification Software, version 6.0 (Philips, Best, The Netherlands). The details regarding speckle tracking analysis have been previously published.[8] For the purposes of the present study, systolic mitral annular velocities and longitudinal wall strain were assessed from the inferoseptal and anterolateral sides of the left ventricle (from the base to the distal part of the particular wall) in an apical 4-chamber view. The interobserver variabilities were 3.7 ± 3.3% and 4.8 ± 5.2%.[8]

The continuous variables are presented as the mean ± SD, and the categorical variables are presented as frequencies and percentages. For the comparisons between 2 time points, a paired sample t test or Wilcoxon signed rank test for 2 related samples was used for normally distributed or skewed data, respectively. For ordinal variables (aortic regurgitation and mitral regurgitation grade), a constant difference between values was assumed. A 2-sided p value of <0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0, software (SPSS, Chicago, Illinois).

Table 1
Baseline characteristics

Variable	Study Population (n = 27)
Age (years)	81 (78–86)
Men	14 (52%)
Body mass index (kg/m^2)	26 ± 4
Body surface area (m^2)	1.84 ± 0.19
Antecedents	
Cerebrovascular events	6 (22%)
Myocardial infarction	6 (22%)
Percutaneous coronary intervention	8 (30%)
Coronary artery bypass	7 (26%)
Co-morbidities	
Chronic obstructive pulmonary disease	8 (30%)
Chronic renal disease	3 (11%)
Peripheral vascular disease	5 (19%)
Atrial fibrillation	6 (22%)
Diabetes mellitus	6 (22%)
Ejection fraction ≤35%	4 (15%)
New York Heart Association status	
I-II	5 (19%)
III-IV	22 (81%)
Logistic EuroSCORE	11 (9–22)

Data are presented as mean ± SD, median (interquartile range), or n (%).

Results

The baseline patient characteristics are summarized in Table 1. The study population consisted of elderly patients with a number of co-morbidities. Of the 27 patients, 4 (15%) had a baseline EF of ≤35%; 8 patients (30%) underwent TAVI using a 26-mm and 19 (70%) using a 29-mm inflow Medtronic-CoreValve. Postdeployment balloon dilation was performed in 3 patients (11%). No patient required a second bioprosthesis as a valve-in-valve bailout.

Before TAVI (1 day before), no patient had a paced rhythm, 1 patient (4%) had a LBBB, and 4 patients (15%) had a left anterior fascicular block. After TAVI (day 6), 4 patients (15%) had a paced rhythm, 15 patients (56%) had a LBBB (14 patients [52%] with a new LBBB), and no patient had a left anterior fascicular block. Therefore, 18 patients (67%) had new conduction abnormalities. With respect to the baseline characteristics, a comparison between the patients with and without new conduction abnormalities did not reveal statistically significant differences. The indication for permanent pacemaker implantation was (in all 4 cases) complete heart block.

The echocardiographic changes after TAVI are listed in Table 2. The mean transaortic gradient decreased from 44 ± 14 to 9 ± 3 mm Hg, and the aortic valve area increased from 0.62 ± 0.20 to 1.65 ± 0.38 cm^2 ($p < 0.001$). A small, nonsignificant decrease in aortic regurgitation and mitral regurgitation severity was observed. Overall, the EF and longitudinal strain did not change significantly; however, the systolic mitral annular velocities improved. The results of a subgroup analysis of LV systolic parameters in relation to new conduction abnormalities are listed in Table 3. In patients with new conduction abnormalities, the EF decreased from 47 ± 12% to 44% ± 10%. In contrast, in those without new conduction abnormalities, the EF increased from 49 ± 12% to 54% ± 12% (Figure 1). The change in

Table 2
Echocardiographic changes after transcatheter aortic valve implantation (TAVI) (n = 27)

Variable	Pre-TAVI	Post-TAVI	p Value
Peak aortic gradient (mm Hg)	75 ± 23	18 ± 7	<0.001
Mean aortic gradient (mm Hg)	44 ± 14	9 ± 3	<0.001
Peak aortic velocity (cm/s)	422 ± 58	210 ± 40	<0.001
Aortic valve area (cm^2)	0.62 ± 0.20	1.65 ± 0.38	<0.001
Aortic regurgitation grade (1–4)	1.8 ± 1.0	1.6 ± 1.2	0.61
Mitral regurgitation grade (1–4)	1.8 ± 0.7	1.6 ± 0.8	0.06
Ejection fraction (%)	47 ± 11	48 ± 12	0.94
Mitral annular velocity (cm/s)			
Inferoseptal	4.0 ± 1.2	5.1 ± 1.7	<0.05
Anterolateral	4.5 ± 1.4	5.6 ± 1.9	<0.05
Longitudinal strain (%)	11 ± 3	12 ± 3	0.64

Data are presented as mean ± SD.

the EF was significantly different among the patients with and without new conduction abnormalities ($p < 0.05$). In addition, in patients without new conduction abnormalities, an improvement was found in the systolic mitral annular velocities and longitudinal strain ($p < 0.05$). In contrast, in patients with new conduction abnormalities, the changes were not significant. In the 4 patients with an EF of ≤35% at baseline, the EF increased from 29 ± 6% to 34% ± 8% ($p = 0.28$)

Discussion

The main finding of the present study was that the induction of new conduction abnormalities after TAVI with the Medtronic-CoreValve was associated with a lack of improvement in LV systolic function.

After surgical aortic valve replacement, the incidence of a new LBBB has been reported to be 6%.[17] In contrast, the need for permanent pacing has been reported to be 3% to 6%.[18] Conduction disorders have been associated with longer hospital stays and more cardiac adverse events within 1 year after surgical aortic valve replacement.[17] To date, no report has been published on the long-term effects of TAVI-induced conduction abnormalities. However, it should be noted that epidemiologic studies have shown increased mortality in patients with a combination of complete heart block or LBBB and structural heart disease.[19]

Conduction disorders occur frequently after TAVI. The anatomic proximity of the aortic valve to the branching atrioventricular bundle, degeneration and calcification of the conduction system, direct trauma by guidewires and catheters and preimplantation balloon valvuloplasty could be possible explanations.[9–12] TAVI using the Medtronic-CoreValve has been associated with a greater incidence of conduction disorders compared to the Edwards SAPIEN valve.[10] This could be explained by the differing sizes of the bioprostheses (height 50 to 51 mm vs 15 to 16 mm) and the different methods of deployment (self expandable vs balloon expandable).[20] The depth of implantation of the Medtronic-CoreValve within the LV outflow track has been reported to predict the occurrence of new conduction abnormalities. In addition, the self-expandable frame per se might produce more permanent trauma to the adjacent tissue by applying continuous pressure on it.[10,20] Pre-existing conduction disorders such as right bundle branch block have been found to predict the need for pacemaker implantation after TAVI.[10] In the present study, no patient had right bundle branch block before or after TAVI. The single patient with LBBB at baseline continued to have LBBB after TAVI. Two of 4 patients with left anterior fascicular block at baseline developed LBBB and 2 developed complete heart block and received a pacemaker.

Most studies investigating the echocardiographic outcome after TAVI used the EF to assess the LV systolic function (Table 4). Not all investigators have reported the EF after TAVI with the Medtronic-CoreValve.[3,4] It seems reasonable to assume that the reason for not reporting the EF after TAVI was the lack of significant changes. Nevertheless, in most studies in which EF was reported, the changes were insignificant, with the exception of subgroup analyses of patients with a low baseline EF in whom significant immediate improvement was found.[6,21] The lack of improvement in the EF was also observed by our group in a previous cohort of 74 patients who were not included in the present study.[7] In contrast, most of the studies on TAVI using the Edwards SAPIEN valve have shown a significant immediate increase in the EF, which was more prominent in patients with a low EF.[1,2,5,22–24] The results of the present study have provided a possible explanation for this discrepancy. Normally, the LV and right ventricular contraction is synchronous. In the presence of LBBB or right apical pacing, right ventricular activation/contraction will precede LV activation/contraction. Consequently, this interventricular asynchrony results in paradoxical septal movement that has been associated with a decrease in global EF, even in the absence of heart failure.[25] The lack of improvement in EF after TAVI with the Medtronic-CoreValve might be because of the greater incidence of new conduction abnormalities, which influence the LV synchronous contraction and, thus, systolic performance. However, although the EF and/or longitudinal strain measurements are useful for the assessment of LV systolic function, they are not synonymous with it. Therefore, the results should be interpreted with caution.

LV systolic function after TAVI was evaluated using Doppler tissue imaging in 2 studies. In the first, involving 8 patients, who had undergone TAVI with the Edwards SAPIEN valve, Bauer et al[23] found a significant increase in the EF, systolic mitral velocities, and longitudinal strain. In the second, involving 39 patients, the EF showed no significant change after TAVI with the Medtronic-CoreValve; however, a small improvement was found in the systolic mitral velocities at 30 days of follow-up, similar to our findings.[6] In our study, the systolic mitral velocities and longitudinal strain increased significantly in the group of patients without new conduction abnormalities. In contrast, in patients with new conduction disorders, the changes were insignificant, in line with the changes in EF. Systolic mitral velocities and longitudinal strain were assessed using STE, which is more sensitive and reproducible than the EF measurements obtained using conventional echocardiography.[8] In addition, the accuracy of STE is greater than that of Doppler tissue imaging. STE directly tracks the speckles on an echo-

Table 3
Left ventricular (LV) systolic function in relation to new conduction abnormalities

Variable	New Conduction Abnormalities			
	No (n = 9)		Yes (n = 18)	
	Pre-TAVI	Post-TAVI	Pre-TAVI	Post-TAVI
Mitral annular velocity (cm/s)				
Inferoseptal	4.3 ± 1.4	6.5 ± 2.2*	3.8 ± 1.0	4.4 ± 0.8
Anterolateral	4.8 ± 1.3	6.6 ± 2.5*	4.4 ± 1.5	5.1 ± 1.4
Longitudinal strain (%)	11 ± 3	13 ± 3*	11 ± 4	11 ± 2
Ejection fraction (%)	49 ± 12	54 ± 12	47 ± 12	44 ± 10†

* $p < 0.05$ versus pre-TAVI in patients without new conduction abnormalities.
† $p < 0.05$ versus post-TAVI in patients without new conduction abnormalities.

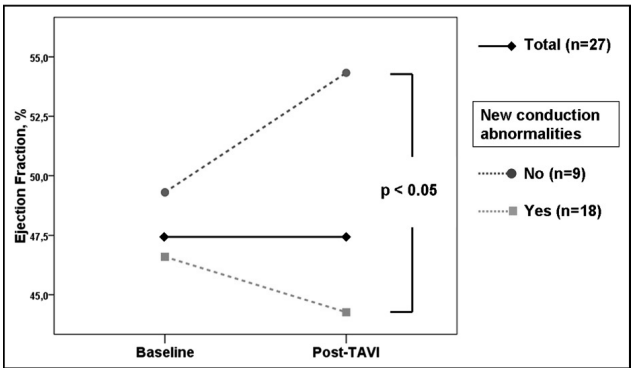


Figure 1. Changes in EF after TAVI. Overall, EF did not change significantly after TAVI *(black line).* In patients without new conduction abnormalities *(blue doted line),* the EF increased but in those with new conduction abnormalities *(green doted line),* EF decreased. The change in EF was significantly different among patients with and without new conduction abnormalities (paired sample *t* test, 2-sided, $p < 0.05$).

Table 4
Reported immediate changes in left ventricular (LV) ejection fraction (EF) after transcatheter aortic valve implantation (TAVI)

Investigator	Year	Device	Patients (n)	Pre-TAVI EF (%)	Post-TAVI EF (%)	p Value
Bauer et al[23]	2004	Edwards	8	48 ± 18	57 ± 12	<0.01
Cribier et al[1]	2006	Edwards	22	45 ± 18	53 ± 14	0.02
Webb et al[2]	2007	Edwards	43	53 ± 15	57 ± 13	<0.0001
Clavel et al[22]	2009	Edwards	50	54 ± 16	59 ± 12	<0.05
Ye et al[5]	2010	Edwards*	71	56 ± 13	61 ± 7	NS
Bauer et al[24]	2010	Edwards	88	48 ± 17	57 ± 15	<0.01
Grube et al[3]	2007	CoreValve	86	54 ± 16	NA	NA
Jilaihawi et al[21]	2009	CoreValve	50	50 ± 14	56 ± 9	0.001
Tzikas et al[7]	2010	CoreValve	71	52 ± 15	52 ± 15	NS
Buellesfeld et al[4]	2010	CoreValve	168	51 ± 16	NA	NA
Gotzmann et al[6]	2010	CoreValve	39	57 ± 10	59 ± 10	NS

* Transapical.
NA = not available; NS, not significant.

cardiogram and, thus, myocardial motion and deformation and is, therefore, independent of the angle of insonation.[8]

The present study was a single-center, prospective study, designed to investigate the immediate effects of TAVI on LV function. Other studies are needed to conclude whether TAVI-induced conduction disorders persist or recover during follow-up. Another limitation was the relatively small number of patients. However, all data (pre- and post-TAVI, including speckle tracking measurements) were 100% complete, allowing a robust paired statistical analysis. Never-

theless, the generalizability of our results should be tested in larger scale studies.

1. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006;47:1214–1223.
2. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, Sinhal A, Carere RG, Munt B, Ricci D, Ye J, Cheung A, Lichtenstein SV. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007;116: 755–763.
3. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr FW, Walther T, Zickmann B, Iversen S, Felderhoff T, Cartier R, Bonan R. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. *J Am Coll Cardiol* 2007;50:69–76.
4. Buellesfeld L, Wenaweser P, Gerckens U, Mueller R, Sauren B, Latsios G, Zickmann B, Hellige G, Windecker S, Grube E. Transcatheter aortic valve implantation: predictors of procedural success—the Siegburg-Bern experience. *Eur Heart J* 2010;31:984–991.
5. Ye J, Cheung A, Lichtenstein SV, Nietlispach F, Albugami S, Masson JB, Thompson CR, Munt B, Moss R, Carere RG, Jamieson WR, Webb JG. Transapical transcatheter aortic valve implantation: follow-up to 3 years. *J Thorac Cardiovasc Surg* 2010;139:1107–1113, 1113.e1.
6. Gotzmann M, Lindstaedt M, Bojara W, Mügge A, Germing A. Hemodynamic results and changes in myocardial function after transcatheter aortic valve implantation. *Am Heart J* 2010;159:926–932.
7. Tzikas A, Piazza N, van Dalen BM, Schultz C, Geleijnse ML, van Geuns RJ, Galema TW, Nuis RJ, Otten A, Gutierrez-Chico JL, Serruys PW, de Jaegere PP. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv* 2010;75:43–49.
8. van Dalen BM, Bosch JG, Kauer F, Soliman OI, Vletter WB, ten Cate FJ, Geleijnse ML. Assessment of mitral annular velocities by speckle tracking echocardiography versus tissue Doppler imaging: validation, feasibility, and reproducibility. *J Am Soc Echocardiogr* 2009;22:1302–1308.
9. Piazza N, Onuma Y, Jesserun E, Kint PP, Maugenest AM, Anderson RH, de Jaegere PP, Serruys PW. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *J Am Coll Cardiol Interv* 2008;1:310–316.
10. Erkapic D, Kim WK, Weber M, Möllmann H, Berkowitsch A, Zaltsberg S, Pajitnev DJ, Rixe J, Neumann T, Kuniss M, Sperzel J, Hamm CW, Pitschner HF. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace* 2010;12:1061–1062.
11. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng GA, Bence J, Logtens E, Kovac J. Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;157:860–866.
12. Baan J Jr, Yong ZY, Koch KT, Henriques JP, Bouma BJ, Vis MM, Cocchieri R, Piek JJ, de Mol BA. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. *Am Heart J* 2010;159:497–503.
13. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H; American Heart Association, Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram. part III: Intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society: endorsed by the International Society for Computerized Electrocardiology. *Circulation* 2009; 119:e235–e240.
14. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and antiarrhythmia devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 51:e1–62.
15. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John Sutton M, Stewart W; American Society of Echocardiography's Nomenclature and Standards Committee; Task Force on Chamber Quantification; American College of Cardiology Echocardiography Committee, American Heart Association, European association of echocardiography, European Society of Cardiology. Recommendations for chamber quantification. *Eur J Echocardiogr* 2006;7:79–108.
16. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, Nihoyannopoulos P, Otto CM, Quinones MA, Rakowski H, Stewart WJ, Waggoner A, Weissman NJ, American Society of Echocardiography. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777–802.
17. El-Khally Z, Thibault B, Staniloae C, Theroux P, Dubuc M, Roy D, Guerra P, Macle L, Talajic M. Prognostic significance of newly acquired bundle branch block after aortic valve replacement. *Am J Cardiol* 2004;94:1008–1011.
18. Huynh H, Dalloul G, Ghanbari H, Burke P, David M, Daccarett M, Machado C, David S. Permanent pacemaker implantation following aortic valve replacement: current prevalence and clinical predictors. *Pacing Clin Electrophysiol* 2009;32:1520–1525.
19. Shen WK, Hammill SC, Hayes DL, Packer DL, Bailey KR, Ballard DJ, Gersh BJ. Long-term survival after pacemaker implantation for heart block in patients > or = 65 years. *Am J Cardiol* 1994;74:560–564.
20. Gutiérrez M, Rodés-Cabau J, Bagur R, Doyle D, DeLarochellière R, Bergeron S, Lemieux J, Villeneuve J, Côté M, Bertrand OF, Poirier P, Clavel MA, Pibarot P, Dumont E. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;158:302–308.
21. Jilaihawi H, Chin D, Spyt T, Jeilan M, Vasa-Nicotera M, Bence J, Logtens E, Kovac J. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic-Corevalve bioprosthesis. *Eur Heart J* 2010;31:857–864.
22. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, De Larochellière R, Doyle D, Masson JB, Bergeron S, Bertrand OF, Rodés-Cabau J. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. *J Am Coll Cardiol* 2009;53:1883–1891.
23. Bauer F, Eltchaninoff H, Tron C, Lesault PF, Agatiello C, Nercolini D, Derumeaux G, Cribier A. Acute improvement in global and regional left ventricular systolic function after percutaneous heart valve implantation in patients with symptomatic aortic stenosis. *Circulation* 2004; 110:1473–1476.
24. Bauer F, Lemercier M, Zajarias A, Tron C, Eltchaninoff H, Cribier A. Immediate and long-term echocardiographic findings after transcatheter aortic valve implantation for the treatment of aortic stenosis: the Cribier-Edwards/Edwards-Sapien valve experience. *J Am Soc Echocardiogr* 2010;23:370–376.
25. Melek M, Esen O, Esen AM, Barutcu I, Onrat E, Kaya D. Tissue Doppler evaluation of intraventricular asynchrony in isolated left bundle branch block. *Echocardiography* 2006;23:120–126.

Electrocardiographic and further predictors for permanent pacemaker requirements after transcatheter aortic valve implantation

Rutger-Jan Nuis[1] and Peter de Jaegere[2]*

[1]Goudsesingel 524, 3011 KR Rotterdam, The Netherlands; and [2]'s Gravendijkwal 230, 3000 CA Rotterdam, The Netherlands

Received 9 April 2010; accepted after revision 14 April 2010; online publish-ahead-of-print 20 May 2010

This editorial refers to 'Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation' by D. Erkapic *et al.*, on page 1188.

Erkapic *et al.*[1] report on the frequency of atrioventricular (AV) conduction abnormalities and new permanent pacemaker (PM) implantation in a series of 50 patients undergoing either Medtronic CoreValve implantation via the femoral artery or the Edwards Sapien valve via a transapical approach. The clinical relevance of this report is related to the fact that conduction abnormalities and implantation of a new PM is currently subject of debate whether this should be considered as a serious adverse event or not. There is a point to do so, since the loss of appropriate conduction and electrical activation of the myocardium in these elderly patients with age-related histological changes in addition to histological changes induced by the increased afterload may affect cardiac output and thus quality of life.

Following surgical aortic valve replacement (SAVR), a new onset left bundle branch block (BBB) has been reported in 16–32% of the patients and new PM implantations are performed in 3–8%.[2–5] The close anatomic relationship between the aortic valve complex and the AV and intraventricular conduction tissue may explain the occurrence of the conduction disturbances following valve procedures.[6] Following transcatheter aortic valve implantation (TAVI), a new onset left BBB and PM implantation with the Medtronic CoreValve Revalving System (CRS) have been reported in up to 65 and 30%, respectively.[7–11] Patients treated with the Edwards–Sapien prosthesis are reported to have left BBB and PM implantation in 20 and 10%, respectively.[9,12]

In a series of 50 patients, Erkapic *et al.* confirmed that a third-degree AV block and subsequent new PM implantation were more common in patients treated with the CRS (16/36, 44%) compared with those who underwent transapical implantation of the Edwards–Sapien bioprosthesis (1/14, 7%). They report that pre-existing right BBB and CRS are predictors for new onset AV block and PM implantation and, therefore, they conclude that using the Edwards device might be more effective in reducing the risk of PM implantation.

These findings and statements need to be interpreted with caution, given the sample size and the complex and multifactorial aetiology of conduction abnormalities during and after TAVI. The only consistency with previous reports which also stem from small-sized single-centre observations is the direction of outcome. This and other studies lack the power and are of insufficient design to adequately interpret the point estimate and the predictive factors of conduction abnormalities. Among others, aetiological factors such as depth of implantation and sizing could not be explored by Erkapic *et al.* In addition, the authors do not report echo-Doppler cardiographic findings. Aortic regurgitation is a well-established predictor of conduction disturbances after surgical valve implantation.[2,4,8] This in turn may lead to a higher frequency of conduction abnormalities during the follow-up period as a result of increased stretch on the conduction tissue. In other words, some potential aetiological factors are correctable (such as depth of implantation and correct sizing) while others are not. Despite the consistency of the direction of outcome, it is premature and fallacious to postulate on the basis of an observation in 50 patients that the occurrence of conduction abnormalities is device related.

Finally, in the absence of criteria of PM implantation, the reported frequency of PM implantation is difficult to interpret. It is astonishing to see that in the presence of an ever increasing number of TAVI procedures, there is a remarkable absence of in-depth knowledge and understanding of the procedure.[13]

Conflict of interest: none declared.

References

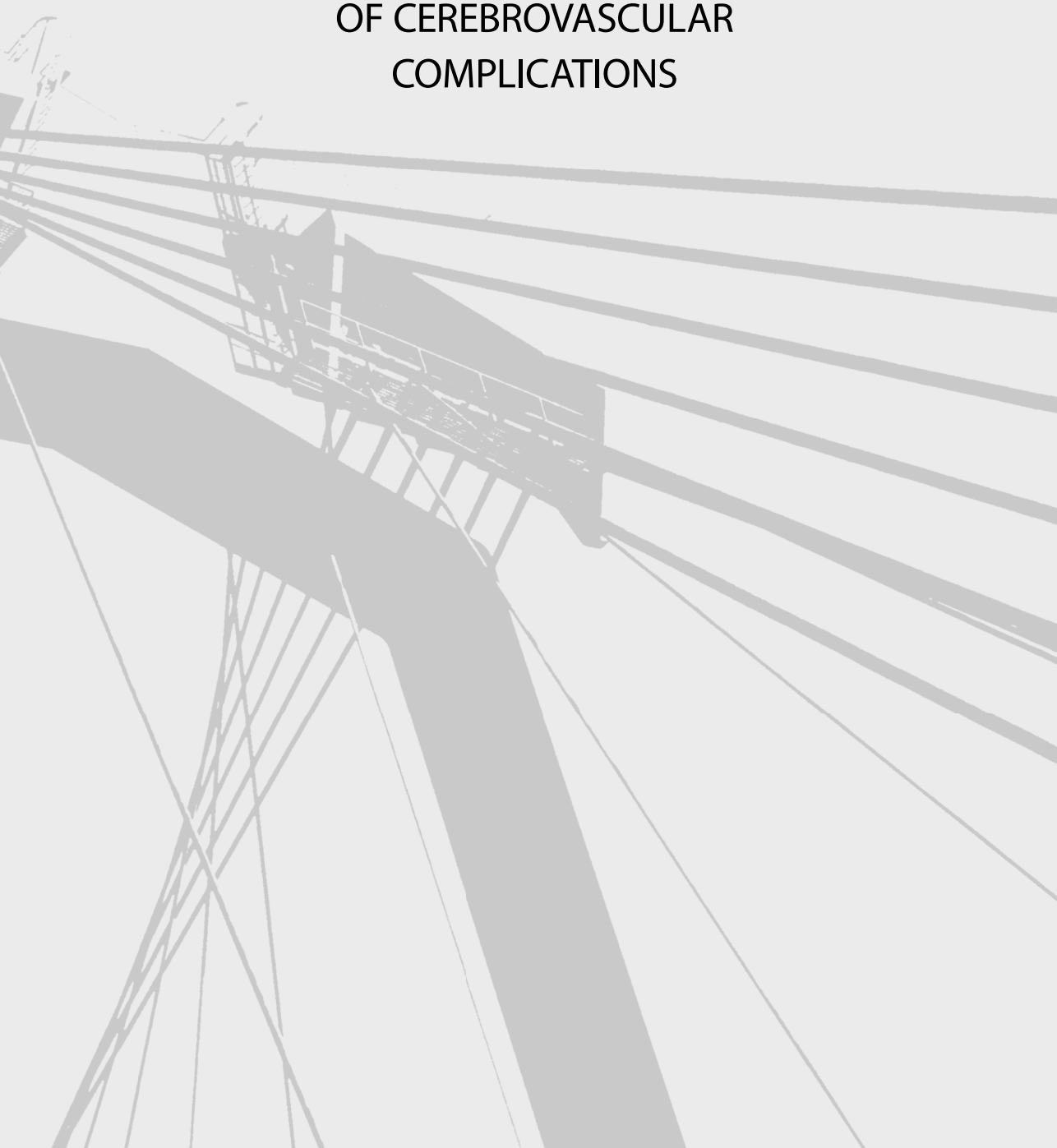
1. Erkapic D, Kim WK, Weber M, Möllmann H, Berkowitsch A, Zaltsberg S *et al.* Electrocardiographic and further predictors for permanent pacemaker requirements after transcatheter aortic valve implantation. *Europace* 2010;**12**:1188–90.

* Corresponding author. Tel: +31 107035656, Email: p.dejaegere@erasmusmc.nl

2. Dawkins S, Hobson AR, Kalra PR, Tang AT, Monro JL, Dawkins KD. Permanent pacemaker implantation after isolated aortic valve replacement: incidence, indications, and predictors. *Ann Thorac Surg* 2008;**85**:108–12.
3. Gordon RS, Ivanov J, Cohen G, Ralph-Edwards AL. Permanent cardiac pacing after a cardiac operation: predicting the use of permanent pacemakers. *Ann Thorac Surg* 1998;**66**:1698–704.
4. Limongelli G, Ducceschi V, D'Andrea A, Renzulli A, Sarubbi B, De Feo M *et al.* Risk factors for pacemaker implantation following aortic valve replacement: a single centre experience. *Heart* 2003;**89**:901–4.
5. Thomas JL, Dickstein RA, Parker FB Jr, Potts JL, Poirier RA, Fruehan CT *et al.* Prognostic significance of the development of left bundle conduction defects following aortic valve replacement. *J Thorac Cardiovasc Surg* 1982;**84**:382–6.
6. Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. *Circ Cardiovasc Interv* 2008;**1**:74–81.
7. Baan J Jr, Yong ZY, Koch KT, Henriques JP, Bouma BJ, Vis MM *et al.* Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. *Am Heart J* 2010;**159**:497–503.
8. Calvi V, Puzzangara E, Pruiti GP, Conti S, Di Grazia A, Ussia GP *et al.* Early conduction disorders following percutaneous aortic valve replacement. *Pacing Clin Electrophysiol* 2009;**32**(Suppl. 1):S126–30.
9. Gutierrez M, Rodes-Cabau J, Bagur R, Doyle D, DeLarochelliere R, Bergeron S *et al.* Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. *Am Heart J* 2009;**158**:302–8.
10. Jilaihawi H, Chin D, Vasa-Nicotera M, Jeilan M, Spyt T, Ng GA *et al.* Predictors for permanent pacemaker requirement after transcatheter aortic valve implantation with the CoreValve bioprosthesis. *Am Heart J* 2009;**157**:860–6.
11. Piazza N, Onuma Y, Jesserun E, Kint PP, Maugenest AM, Anderson RH *et al.* Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. *JACC Cardiovasc Interv* 2008;**1**:310–6.
12. Sinhal AAL, Pasupati S, Humphries KH, Allard M, Martin P, Cheung A, Ye J, Kerr C, Lichenstein SV, Webb JG. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. *J Am Coll Cardiol Intv* 2008;**1**:305–9.
13. de Jaegere PP, Ruiz C, Bonhoeffer P, Vahanian A, Marco J, Serruys PW. Transcatheter aortic valve implantation. Where are we? *EuroIntervention* 2009;**5**:169–71.

PART 3

FREQUENCY AND PATHOPHYSIOLOGY OF CEREBROVASCULAR COMPLICATIONS



CHAPTER 8

Frequency and causes of stroke during or after transcatheter aortic valve implantation

Frequency and Causes of Stroke During or After Transcatheter Aortic Valve Implantation

Rutger-Jan Nuis, MSc[a], Nicolas M. Van Mieghem, MD[a], Carl J. Schultz, MD, PhD[a], Adriaan Moelker, MD, PhD[b], Robert M. van der Boon, MSc[a], Robert Jan van Geuns, MD, PhD[a], Aad van der Lugt, MD, PhD[b], Patrick W. Serruys, MD, PhD[a], Josep Rodés-Cabau, MD[c], Ron T. van Domburg, PhD[d], Peter J. Koudstaal, MD, PhD[e], and Peter P. de Jaegere, MD, PhD[a,*]

Transcatheter aortic valve implantation (TAVI) is invariably associated with the risk of clinically manifest transient or irreversible neurologic impairment. We sought to investigate the incidence and causes of clinically manifest stroke during TAVI. A total of 214 consecutive patients underwent TAVI with the Medtronic-CoreValve System from November 2005 to September 2011 at our institution. Stroke was defined according to the Valve Academic Research Consortium recommendations. Its cause was established by analyzing the point of onset of symptoms, correlating the symptoms with the computed tomography-detected defects in the brain, and analyzing the presence of potential coexisting causes of stroke, in addition to a multivariate analysis to determine the independent predictors. Stroke occurred in 19 patients (9%) and was major in 10 (5%), minor in 3 (1%), and transient (transient ischemic attack) in 6 (3%). The onset of symptoms was early (≤24 hours) in 8 patients (42%) and delayed (>24 hours) in 11 (58%). Brain computed tomography showed a cortical infarct in 8 patients (42%), a lacunar infarct in 5 (26%), hemorrhage in 1 (5%), and no abnormalities in 5 (26%). Independent determinants of stroke were new-onset atrial fibrillation after TAVI (odds ratio 4.4, 95% confidence interval 1.2 to 15.6), and baseline aortic regurgitation grade III or greater (odds ratio 3.2, 95% confidence interval 1.1 to 9.3). In conclusion, the incidence of stroke was 9%, of which >1/2 occurred >24 hours after the procedure. New-onset atrial fibrillation was associated with a 4.4-fold increased risk of stroke. In conclusion, these findings indicate that improvements in postoperative care after TAVI are equally, if not more, important for the reduction of periprocedural stroke than preventive measures during the procedure. **(Am J Cardiol 2012;xx:xxx)**

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered too high a risk for surgical valve replacement (aortic valve replacement).[1] Despite its clinical benefits, TAVI is invariably associated with the risk of clinically manifest transient or irreversible neurologic impairment.[2–5] This can be explained by the various catheter and wire manipulations during TAVI that can result in a cerebral embolus but also by cerebral hypoperfusion due to episodes of hypotension during TAVI resulting from—for instance—rapid right ventricular pacing during aortic balloon valvuloplasty. Also gaseous and atherosclerotic microemboli can provoke ischemia and/or occlusion of deep penetrating arteries of the brain, as recently demonstrated.[5–10] A neurologic deficit can also occur at some point after TAVI for reasons not directly related to the procedure itself, such as is seen in cardiac surgery.[11–13] The understanding of the pathophysiology or cause of stroke during TAVI could help to determine which preventive strategies during and/or after TAVI will most effectively reduce the stroke rates. We, therefore, sought to elucidate the incidence and causes of stroke in a series of 214 consecutive patients by analyzing the time of symptom onset in relation to the procedure and by correlating the symptoms with the computed tomographic (CT)-detected defects in the brain, in addition to the assessment of independent predictors of stroke.

Methods

The study population consisted of all 214 patients (3 intraprocedural deaths excluded) who underwent transfemoral or transsubclavian TAVI with the Medtronic CoreValve System between November 2005 and September 2011 in the Erasmus Thoraxcenter (Rotterdam, The Netherlands). The patient selection criteria and the methods used for Doppler echocardiography have been previously described in detail.[14,15] The treatment strategy (TAVI, aortic valve replacement, or medical therapy) was discussed at a joint cardiothoracic surgical and medical conference.[16]

TAVI was performed with the patient under general

[a]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Department of Radiology, Erasmus Medical Center, Rotterdam, The Netherlands; [c]Department of Cardiology, Quebec Heart and Lung Institute, Quebec City, Quebec, Canada; [d]Department of Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands; [e]Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received December 19, 2011; revised manuscript received and accepted January 17, 2012.

*Corresponding author: Tel: (00) 311-0703-1763; fax: (00) 311-0703-4320.

E-mail address: p.dejaegere@erasmusmc.nl (P.P. de Jaegere).

0002-9149/12/$ – see front matter
doi:10.1016/j.amjcard.2012.01.389

Table 1
Baseline characteristics of patients with and without stroke after transcatheter aortic valve implantation (TAVI)

Variable	Entire Cohort (n = 214)	No Stroke (n = 195)	Stroke (n = 19)	p Value
Age (years)	80 ± 8	80 ± 8	82 ± 6	0.48
Men	107 (50%)	101 (52%)	6 (32%)	0.093
Height (cm)	167 ± 11	167 ± 12	166 ± 8	0.75
Weight (kg)	74 ± 13	74 ± 13	76 ± 12	0.50
Body mass index (kg/m^2)	26.2 ± 4.1	26.1 ± 4.1	27.3 ± 4.3	0.25
Body surface area (m^2)	1.85 ± 0.19	1.85 ± 0.19	1.86 ± 0.17	0.78
New York Heart Association class III or greater	175 (82%)	158 (81%)	17 (90%)	0.54
Previous cerebrovascular event	49 (23%)	47 (24%)	2 (11%)	0.26
Previous myocardial infarction	51 (24%)	49 (25%)	2 (11%)	0.26
Previous coronary artery bypass graft surgery	58 (27%)	55 (28%)	3 (16%)	0.25
Previous percutaneous coronary intervention	56 (26%)	51 (26%)	5 (26%)	1.0
Diabetes mellitus	50 (24%)	46 (24%)	4 (21%)	1.0
Hypertension	126 (59%)	116 (60%)	10 (53%)	0.56
Peripheral vascular disease	26 (21%)	24 (12%)	2 (11%)	1.0
Chronic obstructive pulmonary disease	60 (28%)	53 (27%)	7 (37%)	0.37
Creatinine	95 (76–123)	96 (77–123)	84 (66–112)	0.27
Glomerular filtration rate	57 ± 20	57 ± 20	58 ± 18	0.86
Hemoglobin (g/dl)	12.3 ± 1.7	12.3 ± 1.7	12.1 ± 1.2	0.62
Thrombocyte count	225 ± 67	223 ± 67	244 ± 63	0.21
Prothrombin time (s)	14 ± 8	14 ± 8	14 ± 3	0.89
International normalized ratio	1.21 ± 1.01	1.22 ± 1.05	1.16 ± 0.28	0.83
Atrial fibrillation				
All	64 (30%)	57 (29%)	7 (37%)	0.49
Chronic	44 (21%)	38 (20%)	6 (32%)	0.24
Paroxysmal	20 (9%)	19 (10%)	1 (5%)	1.0
Preprocedural rhythm				
Atrial fibrillation	48 (23%)	44 (23%)	4 (21%)	1.0
Paced	10 (5%)	8 (4%)	2 (11%)	0.22
Porcelain aorta	45 (21%)	38 (20%)	7 (37%)	0.084
Aortic valve area (cm^2)	0.66 ± 0.21	0.66 ± 0.22	0.61 ± 0.16	0.33
Peak velocity	4.3 ± 0.8	4.3 ± 0.8	4.2 ± 0.8	0.76
Mean aortic gradient	45 ± 17	46 ± 17	44 ± 18	0.68
Left ventricular ejection fraction ≤35%	24 (14%)	23 (14%)	1 (6%)	0.70
Aortic regurgitation grade III or greater	42 (20%)	34 (17%)	8 (42%)	0.016
Mitral regurgitation grade III or greater	26 (12%)	23 (12%)	3 (16%)	0.71
Logistic European system for cardiac operative risk evaluation	13.8 (10.0–22.0)	13.8 (10.0–22.8)	12.0 (8.4–16.5)	0.14
Society of Thoracic Surgeon score	5.0 (3.4–7.5)	5.0 (3.4–7.3)	4.3 (3.5–7.5)	0.96
Antiplatelets	105 (49%)	96 (50%)	9 (47%)	1.0
Anticoagulants	67 (32%)	63 (33%)	4 (21%)	0.30

Data are expressed as mean ± SD, median (IQR), or number of patients (%).

anesthesia. The first 5 patients underwent TAVI with a 21F delivery catheter that was inserted into the common femoral (n = 4) or subclavian (n = 1) artery after a surgical cut down. All other patients underwent TAVI with an 18F compatible delivery catheter that was inserted into the common femoral artery using an ultrasound-guided Seldinger technique, except for 5 patients who underwent TAVI by way of the left subclavian artery (surgical exposure and closure).[14] Extracorporal support (extracorporeal membrane oxygenation/TandemHeart, CardiacAssist, Pittsburgh, PA) was used in patients with impaired left ventricular function and a suspected increased risk of periprocedural hemodynamic instability. The subsequent phases of the transfemoral TAVI procedure have been described previously.[17]

Patients who were not taking aspirin and/or clopidogrel received a dose of 80 and 600 mg, respectively, the day before TAVI. Patients who were receiving oral anticoagulant therapy were instructed to stop this treatment 3 days before the procedure. Anticoagulant therapy was replaced by enoxaprin until the day before TAVI in patients with a strict indication for anticoagulant therapy. At admission, a full blood examination was performed, including the prothombin time and international normalized ratio (INR).

After insertion of the arterial sheath, a bolus of 70 U/kg IU unfractionated heparin was administered, followed by additional doses to maintain the activated clotting time at 250 to 350 seconds. The activated clotting time was checked every 30 minutes. The activated partial thromboplastin time was checked within 6 hours after the procedure.

After completion of the procedure (percutaneous or surgical closure of the access site), sedation was stopped, followed by extubation. All patients were transferred to the intensive care unit/cardiac care unit for 12 to 24 hours, or longer if clinically indicated. They were then transferred to the medium care unit until hospital discharge. According to the TAVI protocol, rhythm monitoring by telemetry was

Table 2
Procedural and postprocedural results of patients with and without stroke after transcatheter aortic valve implantation (TAVI)

Variable	No Stroke (n = 195)	Stroke (n = 19)	p Value
Procedural results			
Vascular access			
Surgical—femoral artery	4 (2%)	0	1.0
Surgical—subclavian artery	6 (3%)	0	1.0
Percutaneous—femoral artery	185 (95%)	19 (100%)	0.25
Circulatory support	15 (8%)	3 (16%)	0.21
Additional interventions during TAVI			
Percutaneous transluminal angioplasty iliac artery	6 (3%)	0	1.0
Percutaneous coronary intervention	15 (8%)	2 (11%)	0.65
Prosthesis size* (mm)			
26	59 (30%)	9 (47%)	0.13
29 or 31	135 (69%)	10 (53%)	0.14
Valve/annulus ratio	1.15 ± 0.08	1.16 ± 0.08	0.73
Life-threatening arrhythmia	9 (5%)	0	1.0
Any complication leading to severe hypotension	4 (2%)	0	1.0
Highest activated clotting time (s)	284 ± 87	283 ± 64	0.97
Lowest activated clotting time (s)	221 ± 72	231 ± 73	0.65
Red blood cell transfusions	1.2 ± 2.2	1.3 ± 1.3	0.86
Hemoglobin decrease—uncorrected for red blood cell transfusion (g/dl)	2.0 ± 1.3	2.1 ± 1.0	0.82
Hemoglobin decrease—corrected for red blood cell transfusion (g/dl)	3.2 ± 2.6	3.4 ± 1.7	0.77
Thrombocyte decrease	60 ± 45	60 ± 36	0.98
Therapy-specific results			
Postimplantion balloon dilation	34 (17%)	1 (5%)	0.33
Valve dislodgement†	19 (10%)	1 (5%)	1.0
Valve-in-valve implantation	10 (5%)	1 (5%)	1.0
Duration of procedure (min)	215 ± 75	197 ± 83	0.32
Postprocedural results			
Activated partial thromboplastin time (s)‡	128 ± 92	133 ± 92	0.85
Prosthetic-valve associated results			
Permanent atrial fibrillation§	40 (21%)	6 (33%)	0.23
New atrial fibrillation‖	17 (9%)	5 (26%)	0.032
New left bundle branch block	85 (46%)	6 (32%)	0.31
New permanent pacemaker	41 (21%)	2 (11%)	0.38
Echocardiography			
Peak velocity	2.0 ± 0.5	2.1 ± 0.7	0.59
Mean aortic gradient	9 ± 4	11 ± 6	0.19
Aortic regurgitation grade III or greater	24 (12%)	3 (16%)	0.72
Mitral regurgitation grade III or greater	20 (10%)	3 (16%)	0.44

* One patient did not receive a valve because of aborted TAVI after failed introduction of 18F sheath.
† In all cases, the valve was recaptured and successfully implanted in a second attempt.
‡ Checked within 6 hours after the procedure.
§ Atrial fibrillation before, during, and after TAVI.
‖ Neither preprocedural nor a history of AF.

performed during the hospital stay. All patients received aspirin 80 mg and clopidogrel 75 mg for 6 months. Patients with an indication for oral anticoagulant therapy only received clopidogrel. In these patients, unfractionated heparin was continued after TAVI until adequate INR levels were obtained by acenocoumarol. In-hospital anticoagulant treatment was guided by the prothombin time, INR and activated partial thromboplastin time.

Stroke was defined according to the Valve Academic Research Consortium end point definitions.[18] This implies the following: (1) exclusion of metabolic or toxic encephalopathy or pharmacologic influences explaining the symptoms, in addition to a solely nonfocal neurologic syndrome, (2) execution of a CT study to confirm the clinical diagnosis, (3) the distinction between stroke and transient ischemic attack, and (4) classification of stroke as major or minor according to the degree of disability (modified Rankin score after the procedure and at 30 and 90 days). For patients in whom a modified Rankin score was not documented during the 3 intervals, a detailed chart review was performed to estimate this and accurately classify strokes as major or minor events.

The brain CT scan findings were analyzed using a standard protocol.[19] The cause of stroke was established by (1) analyzing the time of symptom onset, (2) correlating the symptoms with CT-detected defects in the brain, and (3) analyzing the presence of potential coexisting causes of stroke, in addition to multivariate analysis to determine the independent predictors of stroke. Infarcts were categorized as old or new, with the latter

Table 3
Clinical symptoms, computed tomographic (CT) analysis, stroke classification, and atrial fibrillation in patients with stroke after transcatheter aortic valve implantation (TAVI)

Event No.	Pt. No.	Clinical Symptoms				CT Analysis			Classification		AF
		Timing (d)	Symptoms	Duration >24 h	Rankin Score 3 Intervals*	Timing (d)	Infarct Type†	Localization (Hemisphere)	Stroke Type	Ischemic Subtype§	New Onset or Permanent‖
1	7	0	Left-sided hemiparesis, dysarthria-clumsy hand syndrome	No	2; 0; 0	1	Old lacunar	Left	TIA	Lacunar	No
2	16	3	Left-sided hemiparesis, left-sided neglect	Yes	4; 2; 2	3	New cortical (territorial)	Right	Major stroke	Cortical territorial	Permanent
3	17	1¶	Right-sided hemianopia, minimal motor aphasia	Yes	4; 3; 3	2	New cortical (watershed)	Left	Major stroke	Cortical watershed	No
4	18	4	Right leg paresis	No	4; 0; 0	7	Old lacunar	Right + stem	TIA	Uncertain	No
5	19	1¶	Pure motor right hemiparesis	No	4; 0; 0	1	Old lacunar	Left	TIA	Lacunar	Permanent
6	22	5	Left-sided hemiparesis	No	4; 0; 0	6	Negative imaging	Na	TIA	Uncertain	New-onset Day 4
7	26	1	Right-sided hemiparesis	Yes	4; 3; 2	2	Old lacunar (multiple)	Bilateral	Major stroke	Lacunar	No
8	44	0	Buccofacial apraxia	Yes	3; 3; 2	0	Old lacunar	Left	Major stroke	Cortical	Permanent
9	53	0	Right-sided hemiparesis, aphasia	Yes	6; 6; 6	0	Old lacunar; new cortical (watershed)	Left; left	Major stroke	Cortical watershed	Permanent
10	54	2	Right-sided hemiparesis	Yes	2; 0; 0	2	Negative imaging	Na	Minor stroke	Uncertain	Permanent
11	64	6	Right-sided hemiparesis, aphasia	Yes	6; 6; 6	6	Old lacunar; new cortical	Left; left	Major stroke	Cortical territorial	New-onset Day 4
12	86	3	Dysarthria	No	1; 0; 0	3	Old lacunar	Right	TIA	Lacunar	No
13	105	6	Left arm paresis	Yes	3; 2; 2	7	Old lacunar; old cortical (watershed)	Left; right	Major stroke‡	Uncertain	Permanent
14	120	2	Left-sided hemiparesis, dysarthria	Yes	3; 2; 2	2	Old lacunar (multiple)	Left	Major stroke	Lacunar	No
15	137	5	Blurry vision, loss of balance	Yes	4; 4; 3	6	New cortical	Right	Major stroke	Cortical	No
16	146	0	Right-sided hemiparesis	Yes	6; 6; 6	1	New cortical (territorial)	Left	Major stroke	Cortical territorial	New-onset Day 0
17	184	1¶	Right arm paresis	No	2; 0; 0	1	Old cortical	Left	TIA	Uncertain	New-onset Day 0
18	194	0	Right arm paresis, aphasia	Yes	2; 0; 0	6	Subdural hemorrhage	Left	Minor stroke	Na	New-onset Day 12
19	205	2	Hemianopia	Yes	2; 2; 1	2	New cortical (territorial)	Right	Minor stroke	Cortical territorial	No

CT = computed tomography; TIA = transient ischemic attack.
* Modified Rankin score immediately and 30 and 90 days after stroke.
† Not applicable for event number 18 in which a subdural hemorrhage occurred.
‡ Followed by a second stroke 2 days later (CT was performed 1 day after symptom onset and showed no change).
§ Classified by correlating the symptoms with CT-detected defects in the brain.
‖ Atrial fibrillation before, during, and after TAVI.
¶ Symptom onset at day 1 but within 24 hours after TAVI initiation.

further defined as cortical (territorial), cortical watershed, or lacunar infarct.

With respect to the timing of stroke, a distinction was made between stroke that occurred during versus after TAVI. The first was considered directly related to the procedure itself (e.g., due to catheter manipulations or hemodynamic changes) and the second was considered indirectly related to the procedure but not to the procedure itself. Stroke during TAVI was defined if the first symptoms and/or signs were detected ≤24 hours after termination of TAVI. Stroke after TAVI was defined when the first symptoms and/or signs were detected >24 hours after termination of TAVI. The termination of TAVI was defined by the time of vascular closure and hemostasis by either a percutaneous closure device or surgically.

All pre-, intra-, and postprocedural and follow-up data were prospectively collected and entered in a dedicated database as previously described.[17] Porcelain aorta was defined as an extensive circumferential calcification of the thoracic aorta, as assessed by computed tomography and/or fluoroscopy.[20] The blood coagulant status was assessed by collecting the prothombin time, INR, and thrombocyte levels before the procedure. The maximum and minimum activated clotting time levels were documented during the procedure, and the activated partial thromboplastin time was checked within 6 hours after the procedure. Data on red blood cell transfusions were recorded by the institution's blood bank laboratory and used to determine the corrected hemoglobin decrease within 24 hours after TAVI according to the modified Landefeld equation.[21,22] In this equation, 1 U of packed red blood cells is considered to represent 1 g/dl of hemoglobin; therefore, the net hemoglobin decrease corresponds to the addition of the number of packed red blood cells to the baseline minus the measured nadir hemoglobin level.

The occurrence and timing of new atrial fibrillation (AF) after TAVI—defined as any episode of AF lasting >30 seconds in patients with no history of chronic/paroxysmal AF—was determined by collecting the baseline and all postoperative 12-lead ECGs and 24-hour telemetry rhythm strips.[23,24] Follow-up information was prospectively collected during the structured outpatient clinic visits after hospital discharge. In addition, the survival and cause of death was obtained every 6 months by contacting the Dutch Civil Register.

The categorical variables are presented as frequencies and percentages and were compared using the chi-square test or Fisher's exact test. The normality of distributions was assessed with the Shapiro-Wilk test. Normal and skewed continuous variables are presented as the mean ± SD and median (interquartile range [IQR]), respectively. A comparison of continuous variables was done using Student *t* tests or Wilcoxon's rank sum test, when appropriate. Univariate analysis was performed to characterize the patients with and without stroke. Multivariate logistic regression analysis was performed to determine the predictive factors for stroke or transient ischemic attack, taking into account the restricted number of events. Preprocedural AF rhythm was included in the model. A 2-sided p value <0.05 was considered to indicate significance, and all statistical analyses were performed with SPSS software, version 17 (SPSS, Chicago, IL).

Results

The baseline characteristics and procedural details are listed in Tables 1 and 2. The incidence of stroke was 9% (19 patients) and—in accordance with the Valve Academic Research Consortium criteria—consisted of major stroke in 10 patients (5%), minor in 3 (1%), and transient ischemic attack in 6 (3%).

In all patients, except 1, who experienced a subdural hemorrhage (event number 18), the stroke was ischemic (Table 3) and occurred early (≤24 hours after TAVI) in 8 patients (42%) and was delayed (>24 hours, mean 3.5 days after TAVI) in 11 (58%). CT scan analysis of the brain revealed that stroke consisted of a cortical infarct in 8 patients (of which 4 were territorial and 2 were watershed) and a lacunar infarct in 5. In descending order of odds, new AF (odds ratio 4.4, 95% confidence interval 1.2 to 15.6) and baseline aortic regurgitation grade III or greater (odds ratio 3.2, 95% confidence interval 1.1 to 9.3) were identified as independent predictors. New AF occurred in 22 (14%) at a median of 2 days (IQR 1 to 4.5) after TAVI and resolved spontaneously within 12 hours in 8 patients (36%). Seven patients (32%) received pharmacologic treatment (n = 6) or electric (n = 1) conversion. Antithrombotic therapy (aspirin and clopidogrel) without anticoagulant therapy was maintained in 7 patients (36%) in whom the risk of bleeding was considered greater than the risk of thromboembolism. None of the 5 patients with new AF who experienced a stroke had received anticoagulant therapy.

The hospital or 30-day mortality rate in patients with a stroke was 16% (n = 3) and was 6% (n = 15) in patients without a stroke (p = 0.14). The cause of death in these 3 patients was the neurologic event itself. Clinical follow-up was complete for all patients (median 13 months, IQR 6 to 30). During follow-up, 3 patients developed a fatal stroke (2 hemorrhagic, 1 uncertain) and 6, a nonfatal stroke (all ischemic).

Discussion

The present study of 214 consecutive patients who underwent TAVI has shown that a clinically manifest neurologic impairment occurred in 19 patients (9%), with most events (n = 11; 58%) occurring >24 hours after TAVI at a mean of 3.5 days. Furthermore, we found that new-onset AF after TAVI was associated with a 4.4-fold greater risk of stroke.

Our observation that most events occur after and not during TAVI is consistent with the findings of the Canadian multicenter TAVI registry (345 patients) in which procedural stroke was reported in 0.6% of the patients and stroke at 30 days in 2.3%.[20] Supplementary information from the Placement of AoRtic TraNscathetER Valves (PARTNER) Cohort B study revealed that 5 of the 11 strokes occurred at day 0 or 1 after TAVI (45%) and 6 (55%) at day 2 or later.[2] Of note, in cardiac surgery, ≤65% of the neurologic events are seen after the operation.[11–13] In addition, patients undergoing TAVI appear to be at a high risk of stroke, irre-

spective of any intervention (cardiac or otherwise), as indicated by the rather frequent occurrence of stroke during follow-up, such as seen in this and other studies.[2,25]

That most strokes occurred after TAVI indicate that—in a number of patients—there is no direct relation between the intervention and the cerebral complication. These findings suggest that clinical, rather than technical or procedural, factors play a more important role in the occurrence of stroke during TAVI and that, therefore, preventive measures should, above all, be directed at improved postoperative management. It also suggests that endovascular embolic protection devices used during the procedure—if safe and effective—might reduce the stroke rates in only about ½ of the patients.[26] This is further supported by the fact that 26% of the strokes were lacunar, which is widely regarded as caused by cerebral hypoperfusion in the presence of local atherosclerosis. This implies that all efforts should be made during TAVI to maintain adequate brain perfusion. In this respect, TAVI without balloon valvuloplasty, such as proposed by Grube et al,[27] might be beneficial if this technique does not induce the dislodgement of calcified atherosclerotic emboli, while advancing the prosthesis in the aortic annulus.[27]

The role of improved postoperative care is supported by the finding that new AF after TAVI was the main determinant of stroke. Because the present study lacks the power to perform a comprehensive multivariate analysis, other factors might have remained undetected. The reason patients with aortic regurgitation grade ≥3 before TAVI are at increased risk of stroke remains to be elucidated. Although this might be a finding by chance owing to the small sample size and the absence of a pathophysiologic concept, these patients possibly had a more impaired and/or dilated left atrium, which is known to predict new AF after cardiac surgery and also after TAVI.[28,29] Scant information is available on new AF after TAVI. In the PARTNER cohort B study, new AF was seen in 1 of the 151 patients with no previous AF (0.7%), who underwent transfemoral TAVI.[2] The incidence of new AF in the PARTNER Cohort A study was 7.5% after transfemoral and 11.5% after transapical TAVI.[3] Similar to the results of Amat-Santos et al,[29] who found new AF in 16% of the patients undergoing transfemoral TAVI, we found new AF in 22 (14%) of the 154 patients with no previous AF.[29] In accordance with the findings from Amat-Santos et al,[29] the data of our study also indicate that suboptimal anticoagulant therapy in patients with new AF plays a role in the occurrence of stroke because none of the 5 patients with new AF who experienced a stroke received anticoagulant therapy. No clear guidelines are available on anticoagulation therapy after short episodes of AF after cardiac surgery.[24] However, patients undergoing TAVI are at high risk of thromboembolism when atrial fibrillation occurs (median $CHADS_2$ score 3 [IQR 2 to 4] in patients with new AF). Therefore, immediate anticoagulant therapy should probably be implemented in these patients on the diagnosis of AF.

The results of the multivariate analysis must be interpreted in the context of the number of patients included in the present study. In the control group, 17 of the 195 patients had new AF compared to 5 of the 19 in the stroke group. One patient less or more in 1 group can significantly affect the results of the analysis. However, it is quite conceivable that new AF is an important cause of stroke in the present reported patients, because new AF is known to be associated with an increased risk of cardioembolism.[29,30] New AF preceded the first signs of neurologic impairment in all patients with an ischemic stroke (Table 3) and in 3 of the 6 patients with a (territorial) cortical infarct—typically of thrombotic origin—were preceded by new AF and no patient with a lacunar infarct—typically not caused by a large thrombus or embolus—had new AF after TAVI.

The main limitation of the present study was the number of patients, thereby limiting the precision of the observed point estimate of the incidence of stroke and the power and robustness of the multivariate analysis. In particular, the lack of statistical correction in the present study might have influenced the significance of the predictors of stroke; therefore, these findings merit confirmation in larger series. Furthermore, we lacked a standardized, complete diagnostic workup for all patients with stroke. For instance, duplex or angiography of the carotid and vertebral arteries was not performed in the large majority of the present series of patients.

1. Buellesfeld L, Windecker S. Transcatheter aortic valve implantation: the evidence is catching up with reality. *Eur Heart J* 2011;32:133–137.
2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
3. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364: 2187–2198.
4. Daneault B, Kirtane AJ, Kodali SK, Williams MR, Genereux P, Reiss GR, Smith CR, Moses JW, Leon MB. Stroke associated with surgical and transcatheter treatment of aortic stenosis: A comprehensive review. *J Am Coll Cardiol* 2011;58:2143–2150.
5. Rodés-Cabau J, Dumont E, Boone RH, Larose E, Bagur R, Gurvitch R, Bédard F, Doyle D, De Larochellière R, Jayasuria C, Villeneuve J, Marrero A, Côté M, Pibarot P, Webb JG. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. *J Am Coll Cardiol* 2011;57:18–28.
6. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R, Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation* 2010;121: 870–878.
7. Ghanem A, Müller A, Nähle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G, Thomas D. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol* 2010;55:1427–1432.
8. Arnold M, Schulz-Heise S, Achenbach S, Ott S, Dorfler A, Ropers D, Feyrer R, Einhaus F, Loders S, Mahmoud F, Roerick O, Daniel WG, Weyand M, Ensminger SM, Ludwig J. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. *JACC Cardiovasc Intv* 2010;3:1126–1132.
9. Astarci P, Glineur D, Kefer J, D'Hoore W, Renkin J, Vanoverschelde JL, El Khoury G, Grandin C. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. *Eur J Cardiothorac Surg* 2011;40:475–479.

10. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S, Greenwood JP. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. *Heart* 2012;98:18–23.
11. Hogue CW Jr, Murphy SF, Schechtman KB, Dávila-Román VG. Risk factors for early or delayed stroke after cardiac surgery. *Circulation* 1999;100:642–647.
12. Filsoufi F, Rahmanian PB, Castillo JG, Bronster D, Adams DH. Incidence, imaging analysis, and early and late outcomes of stroke after cardiac valve operation. *Am J Cardiol* 2008;101:1472–1478.
13. Naylor AR, Mehta Z, Rothwell PM, Bell PR. Carotid artery disease and stroke during coronary artery bypass: a critical review of the literature. *Eur J Vasc Endovasc Surg* 2002;23:283–294.
14. Nuis RJ, van Mieghem NM, van der Boon RM, van Geuns RJ, 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.
15. Schultz CJ, Tzikas A, Moelker A, Rossi A, Nuis RJ, Geleijnse MM, van Mieghem N, Krestin GP, de Feyter P, Serruys PW, de Jaegere PP. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the Medtronic CoreValve prosthesis. *Catheter Cardiovasc Interv* 2011;78:446–455.
16. Nuis RJ, Dager AE, van der Boon RM, 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* 2012;20:16–23.
17. 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. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve system in patients with aortic stenosis. *Eur Heart J* 2011;32:2067–2074.
18. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the valve academic Research Consortium. *J Am Coll Cardiol* 2011;57:253–269.
19. Paciaroni M, Silvestrelli G, Caso V, Corea F, Venti M, Milia P, Tambasco N, Parnetti L, Gallai V. Neurovascular territory involved in different etiological subtypes of ischemic stroke in the Perugia stroke registry. *Eur J Neurol* 2003;10:361–365.
20. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010;55:1080–1090.
21. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization: the EPILOG Investigators. *N Engl J Med* 1997;336:1689–1696.
22. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med* 1987; 82:703–713.
23. Murdock DK, Rengel LR, Schlund A, Olson KJ, Kaliebe JW, Johnkoski JA, Riveron FA. Stroke and atrial fibrillation following cardiac surgery. *WMJ* 2003;102:26–30.
24. Wann LS, Curtis AB, January CT, Ellenbogen KA, Lowe JE, Estes NA III, Page RL, Ezekowitz MD, Slotwiner DJ, Jackman WM, Stevenson WG, Tracy CM, Fuster V, Rydén LE, Cannom DS, Le Heuzey JY, Crijns HJ, Olsson SB, Prystowsky EN, Halperin JL, Tamargo JL, Kay GN, Jacobs AK, Anderson JL, Albert N, Hochman JS, Buller CE, Kushner FG, Creager MA, Ohman EM, Ettinger SM, Guyton RA, Tarkington LG, Yancy CW, Accf, Aha, Guyton RA, Tarkington LG, Halperin JL, Yancy CW; ACCF/AHA/HRS. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2011;57:223–242.
25. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation* 2011;124:425–433.
26. Nietlispach F, Wijesinghe N, Gurvitch R, Tay E, Carpenter JP, Burns C, Wood DA, Webb JG. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Intv* 2010;3:1133–1138.
27. Grube E, Naber C, Abizaid A, Sousa E, Mendiz O, Lemos P, Kalil Filho R, Mangione J, Buellesfeld L. Feasibility of transcatheter aortic valve implantation without balloon pre-dilation: a pilot study. *JACC Cardiovasc Intv* 2011;4:751–757.
28. Osranek M, Fatema K, Qaddoura F, Al-Saileek A, Barnes ME, Bailey KR, Gersh BJ, Tsang TS, Zehr KJ, Seward JB. Left atrial volume predicts the risk of atrial fibrillation after cardiac surgery: a prospective study. *J Am Coll Cardiol* 2006;48:779–786.
29. Amat-Santos IJ, Rodés-Cabau J, Urena M, Delarochellière R, Doyle D, Bagur R, Villeneuve J, Côté M, Nombela-Franco L, Philippon F, Pibarot P, Dumont E. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol* 2012;59:178–188.
30. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22:983–988.

CHAPTER 9

Timing, predictive factors, and prognostic value of cerebrovascular events in a large cohort of patients undergoing trancatheter aortic valve implantation

Timing, Predictive Factors, and Prognostic Value of Cerebrovascular Events in a Large Cohort of Patients Undergoing Transcatheter Aortic Valve Implantation

Luis Nombela-Franco, MD; John G. Webb, MD; Peter P. de Jaegere, MD, PhD; Stefan Toggweiler, MD; Rutger-Jan Nuis, MSc; Antonio E. Dager, MD; Ignacio J. Amat-Santos, MD; Anson Cheung, MD; Jian Ye, MD; Ronald K. Binder, MD; Robert M. van der Boon, MSc; Nicolas Van Mieghem, MD; Luis M. Benitez, MD; Sergio Pérez, MD; Javier Lopez, MD, PhD; José A. San Roman, MD, PhD; Daniel Doyle, MD; Robert DeLarochellière, MD; Marina Urena, MD; Jonathon Leipsic, MD; Eric Dumont, MD; Josep Rodés-Cabau, MD

Background—The objective of this study was to evaluate the timing, predictive factors, and prognostic value of cerebrovascular events (CVEs) after transcatheter aortic valve implantation.

Methods and Results—The study included 1061 consecutive patients who underwent transcatheter aortic valve implantation with a balloon-expandable (64%) or self-expandable (36%) valve. CVEs were classified as acute (≤24 hours), subacute (1–30 days), or late (>30 days). CVEs occurred in 54 patients (5.1%; stroke, 4.2%) within 30 days after transcatheter aortic valve implantation (acute in 54% of cases). The predictors of acute CVEs were balloon postdilation of the valve prosthesis (odds ratio, 2.46; 95% confidence interval,1.07–5.67) and valve dislodgment/embolization (odds ratio, 4.36; 95% CI, 1.21–15.69); new-onset atrial fibrillation (odds ratio, 2.76; 95% CI, 1.11–6.83) was a predictor of subacute CVEs. Late CVEs occurred in 35 patients (3.3%; stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (2.84; 95% CI, 1.46–5.53), peripheral vascular disease (hazard ratio, 2.02; 95% CI, 1.02–3.97), and prior cerebrovascular disease (hazard ratio, 2.04; 95% CI, 1.01–4.15). Major stroke was associated with 30-day (odds ratio, 7.43; 95% CI, 2.45–22.53) and late (hazard ratio, 1.75; 95% CI, 1.01–3.04) mortality.

Conclusions—In a large cohort of patients undergoing transcatheter aortic valve implantation, the rates of acute and subacute CVEs were 2.7% and 2.4%, respectively. While balloon postdilation and valve dislodgment/embolization were the predictors of acute CVEs, new-onset atrial fibrillation determined a higher risk for subacute events. Late events were determined mainly by a history of chronic atrial fibrillation and peripheral and cerebrovascular disease. The occurrence of major stroke was associated with increased early and late mortality. These results provide important insights for the implementation of preventive measures for CVEs after transcatheter aortic valve implantation. **(*Circulation*. 2012;126: 3041-3053.)**

Key Words: aortic valve stenosis ■ heart valve prosthesis implantation ■ heart valves ■ stroke

Transcatheter aortic valve implantation (TAVI) has recently emerged as the preferred therapy for inoperable patients with severe aortic stenosis and as an alternative to surgical aortic valve replacement in high-risk patients.[1] Although TAVI has been associated with a very high procedural success rate, the occurrence of cerebrovascular events (CVEs) has appeared to be one of the most worrisome complications associated with these procedures. Several cerebral magnetic resonance imaging studies have shown a very high incidence (66%–86%) of new ischemic defects after TAVI regardless of the transcatheter valve type (balloon-expandable, self-expandable) and approach (transfemoral, transapical).[2] Although these new cerebral defects are silent in most cases, the incidence of clinically apparent stroke after TAVI has been ≈3.5% (ranging from 1.2%–6.7%),[3–11] one of the highest ever reported in the field of interventional

Received April 9, 2012; accepted October 15, 2012.

From the Quebec Heart and Lung Institute, Laval University, Quebec City, QC, Canada (L.N.-F., D.D., R.D., M.U., E.D., J.R.-C.); St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada (J.G.W., S.T., A.C., J.Y., R.K.B., J.L.); Thoraxcenter-Erasmus Medical Center, Rotterdam, the Netherlands (P.P.d.J., R.-J.N., R.M.v.d.B., N.V.M.); Angiografia de Occidente S.A., Cali, Colombia (A.E.D., L.M.B., S.P.); and Hospital Clinico Universitario de Valladolid, Valladolid, Spain (I.J.A.-S., J.L., J.A.S.R.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.112.110981/-/DC1.

Correspondence to Josep Rodés-Cabau, MD, Department of Cardiology, Quebec Heart and Lung Institute, Laval University, 2725 Chemin Ste-Foy, Quebec City, QC, Canada. E-mail josep.rodes@criucpq.ulaval.ca

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.110981**

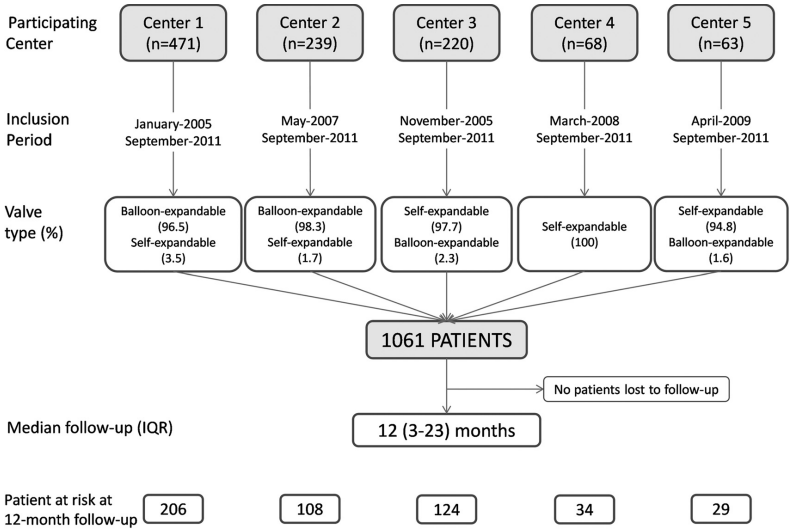


Figure 1. Study flow diagram of patients who underwent transcatheter valve implantation of each participating center. IQR indicates interquartile range.

cardiology. In addition, the Placement of Aortic Transcatheter Valve Trial (PARTNER) showed that TAVI was associated with a higher rate of CVEs compared with medical treatment/balloon valvuloplasty or aortic valve replacement.[10,11] A better knowledge of the mechanisms determining this high rate of CVEs after TAVI would therefore be crucial for the implementation of appropriate preventive measures. Transcranial Doppler studies have shown that cerebral emboli can occur any time during the TAVI procedure but seem to be more frequent during valve prosthesis positioning and implantation.[12–15] However, about half the periprocedural CVEs occur >24 hours after the TAVI procedure,[2] suggesting that mechanisms other than those directly related to the catheter, wire, and valve prosthesis manipulation are also involved in the 30-day CVE rate. A few studies including a relatively limited number of patients have suggested the presence of smaller valve areas, balloon postdilation, multiple valve implantation attempts, and atrial arrhythmias as factors determining a higher rate of early CVEs after TAVI.[16–20] However, the relatively low absolute number of events in these studies might have precluded an accurate analysis of the predictors of CVEs. In addition, no data exist on the baseline and procedural variables associated with CVEs occurring in the acute phase (≤24 hours) after TAVI compared with those occurring later. Finally, it is well known that stroke significantly affects survival and quality of life after aortic valve replacement,[21,22] but few data exist on the independent prognostic value of this complication at short-term and midterm follow-up in a large cohort of TAVI patients.[7] Therefore, the objective of this study was to determine the timing, predictive factors, and prognostic value of CVEs in a large cohort of consecutive patients undergoing TAVI.

Editorial see p 2921
Clinical Perspective on p 3053

Methods

Study Population and TAVI Procedures

A total of 1061 consecutive patients with symptomatic severe aortic stenosis who underwent TAVI with either balloon-expandable or self-expandable valves in 5 centers were included (Figure 1). Eligibility for TAVI was established at each center and based on the consensus of a local multidisciplinary team composed of interventional cardiologists and cardiac surgeons. Baseline clinical and echocardiography data were prospectively gathered in each participating center. Comorbidities were defined according to the Society of Thoracic Surgeons criteria. The degree of calcification of the thoracic aorta was assessed by computed tomography and/or fluoroscopy, and the presence of severely calcified aorta was recorded in all patients. The presence of complex atheroma aortic plaques was determined by transesophageal echocardiography (data available in 689 patients) and defined as large plaques (≥4 mm in thickness), plaques with ulceration, or mobile components.[23] Selection of the access route was based on the appropriateness of the iliofemoral axis. The patients treated by transfemoral/subclavian approach received dual antiplatelet therapy (aspirin plus clopidogrel) the day before TAVI. The patients treated by transapical/transaortic approach received single antiplatelet therapy (aspirin) before the procedure except if the patient had a prior medical condition for which dual antiplatelet therapy was required. Patients who were receiving oral anticoagulation therapy were instructed to stop it 3 days before the procedure, and single or dual antiplatelet therapy was administrated. Intraprocedural anticoagulation was achieved by a dose of unfractionated heparin (70–100 U/kg) at the beginning of the procedure and adjusted by activated clothing time (>250 seconds) during the procedure. Antithrombotic treatment after TAVI consisted of aspirin (indefinitely) plus clopidogrel (3–6 months) unless contraindicated. If anticoagulation was indicated for any other reason, oral anticoagulant therapy was administered (with or without single or dual

Table 1. Baseline Characteristics of the Study Population, Overall and According to the Occurrence of 30-Day Cerebrovascular Events After Transcatheter Aortic Valve Implantation

		≤30-Day Cerebrovascular Event		
Variables	All (n=1061)	Yes (n=54)	No (n=1007)	*P*
Baseline variables				
Age, y	81±8	82±6	81±8	0.155
Male sex, n (%)	538 (50.7)	22 (40.7)	516 (51.2)	0.133
BMI, kg/m^2	26.0±5.0	26.7±4.7	26.0±5.0	0.337
Diabetes mellitus, n (%)	312 (29.4)	22 (40.7)	290 (28.8)	0.061
Previous heart failure, n (%)	721 (68.0)	32 (59.3)	689 (68.4)	0.160
Hypertension, n (%)	790 (74.5)	39 (72.2)	751 (74.6)	0.699
NYHA functional class III–IV, n (%)	886 (83.5)	49 (90.7)	837 (83.1)	0.141
Chronic atrial fibrillation, n (%)	276 (26.0)	15 (27.8)	261 (25.9)	0.765
Coronary artery disease, n (%)	686 (64.7)	32 (59.3)	654 (64.9)	0.394
Previous myocardial infarction, n (%)	377 (35.6)	16 (29.6)	361 (35.9)	0.347
Prior CABG, n (%)	320 (30.2)	14 (25.9)	306 (30.4)	0.486
Cerebrovascular disease, n (%)	191 (18.1)	9 (16.7)	182 (18.2)	0.778
Peripheral vascular disease, n (%)	278 (26.2)	9 (16.7)	269 (26.7)	0.116
COPD, n (%)	310 (29.2)	19 (35.2)	291 (28.9)	0.322
Severely calcified aorta, n (%)	193 (18.4)	14 (25.9)	179 (18.0)	0.142
eGFR, mg/min	60.1±27.8	58.8±43.3	60.2±26.7	0.726
STS-PROM score, %	6.5 (4.3–9.7)	6.4 (3.8–10.4)	6.5 (4.4–9.7)	0.578
$CHADS_2$ score	2.9±1.2	3.0±1.3	2.9±1.2	0.711
Echocardiography data				
Mean aortic gradient, mm Hg	43±16	46±18	43±16	0.281
Aortic valve area, cm^2	0.66±0.19	0.61±0.18	0.66±0.19	0.110
LVEF <40%, n (%)	235 (22.1)	8 (14.8)	227 (22.5)	0.193
Complex aortic plaques†, n (%)	119 (17.3)	6 (21.4)	113 (17.1)	0.608
Periprocedural data, n (%)				
Learning curve*				0.098
First half	532 (50.1)	33 (6.2)	499 (93.8)	
Second half	529 (49.9)	21 (4.0)	508 (96.0)	
Approach				0.722
Transfemoral	726 (68.4)	40 (74.1)	686 (68.1)	
Transapical	322 (30.3)	14 (25.9)	308 (30.6)	
Subclavian	9 (0.8)	0	9 (0.9)	
Transaortic	4 (0.4)	0	4 (0.4)	
Prosthesis type				0.236
Cribier-Edwards	57 (5.4)	3 (5.6)	54 (5.4)	
Edwards Sapien	388 (36.6)	20 (37.0)	368 (36.5)	
Sapien XT	234 (22.1)	6 (11.1)	228 (22.6)	
CoreValve (second generation)	5 (0.5)	0	5 (0.5)	
CoreValve (third generation)	349 (32.9)	24 (44.4)	325 (32.3)	
St. Jude Portico	7 (0.7)	1 (1.9)	6 (0.6)	
Prosthesis size, mm				0.981
20	3 (0.3)	0	3 (0.3)	
23	305 (29.3)	15 (27.8)	290 (29.4)	
26	502 (48.3)	28 (51.9)	474 (48.1)	
29	228 (21.9)	11 (20.4)	217 (22.0)	
31	2 (0.2)	0	2 (0.2)	

(*Continued*)

Table 1. Continued

Variables	All (n=1061)	≤30-Day Cerebrovascular Event		P
		Yes (n=54)	No (n=1007)	
Ratio of prosthesis size to annulus size	1.13±0.08	1.13±0.07	1.13±0.08	0.909
Balloon postdilation	189 (17.8)	16 (29.6)	173 (17.2)	0.020
Valve dislodgment/embolization	44 (4.1)	4 (7.4)	40 (4.0)	0.217
Need for a second valve	33 (3.1)	2 (3.7)	31 (3.1)	0.797
Need for hemodynamic support or severe maintained hypotension	54 (5.1)	4 (7.4)	50 (5.0)	0.431
Major vascular complication	100 (9.4)	3 (5.6)	97 (9.6)	0.318
New-onset atrial fibrillation	127 (12.0)	12 (22.2)	115 (11.4)	0.017
Antithrombotic treatment, n (%)				
Baseline				0.135
None	156 (14.7)	13 (24.1)	143 (14.2)	
Single antiplatelet therapy	431 (40.6)	22 (40.7)	409 (40.6)	
Dual antiplatelet therapy	163 (15.4)	5 (9.3)	158 (15.7)	
Anticoagulation therapy	187 (17.6)	7 (13.0)	180 (17.9)	
Single antiplatelet+anticoagulation therapy	111 (10.5)	5 (9.3)	106 (10.5)	
Triple therapy	13 (1.2)	2 (3.7)	11 (1.1)	
Discharge				0.379
None	18 (1.8)	1 (2.1)	17 (1.8)	
Single antiplatelet therapy	84 (8.5)	1 (2.1)	83 (8.9)	
Dual antiplatelet therapy	539 (54.8)	26 (54.2)	513 (54.8)	
Anticoagulation therapy	54 (5.5)	5 (10.4)	49 (5.2)	
Single antiplatelet+anticoagulation therapy	249 (25.3)	12 (25.0)	237 (25.3)	
Triple therapy	40 (4.1)	3 (6.3)	37 (4.0)	
30-d Follow-up				0.160
None	11 (1.2)	1 (2.3)	10 (1.2)	
Single antiplatelet therapy	75 (8.4)	1 (2.3)	74 (8.7)	
Dual antiplatelet therapy	492 (55.0)	22 (50.0)	470 (55.2)	
Anticoagulation therapy	56 (6.3)	6 (13.6)	50 (5.9)	
Single antiplatelet+anticoagulation therapy	228 (25.5)	11 (25.0)	217 (25.5)	
Triple therapy	33 (3.7)	3 (6.8)	30 (3.5)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

antiplatelet therapy). Data on procedural success and periprocedural complications defined according to the Valve Academic Research Consortium (VARC) criteria were prospectively collected in each participating center.[24]

Cerebrovascular Events

Cerebrovascular events were defined according to the VARC criteria and categorized as transient ischemic attack or stroke.[24] Transient ischemic attack was defined as an episode of neurological dysfunction that lasted <24 hours without association of cerebral infarction on imaging. Clinical stroke was defined as an acute neurological dysfunction lasting >24 hours and/or with evidence of infarction on imaging and further classified according to the modified Rankin Scale as major stroke (modified Rankin Scale score ≥2 at 30 days) or minor stroke (modified Rankin Scale score <2 at 30 days). The modified Rankin Scale was calculated prospectively on the publication of the VARC definitions (January 2011; 21% of the study population) and retrospectively in patients undergoing TAVI before the publication of the VARC definitions.[24] A detailed chart review was done to calculate the modified Rankin Scale score and to classify strokes as major or minor events. CVEs were also classified according to the timing with respect to the TAVI procedure as acute (≤24 hours), subacute (1–30 days), and late (>30 days) events. The diagnosis of CVE was always confirmed by a neurologist, and a neuroimaging procedure was performed in all cases.

Follow-Up

Clinical follow-up and postdischarge events were carried out in clinical visits and/or through phone contact. Referring cardiologists, general practitioners, and patients' families were contacted whenever necessary for further information. Patients were followed up at 1 to 3 months, at 12 months, and yearly thereafter in all participating centers. Mortality and the occurrence of CVEs at any time during the follow-up period were prospectively recorded by each participating center. All clinical events were defined according to the VARC criteria.[24]

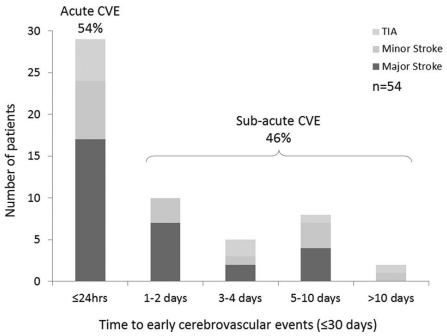


Figure 2. Timing of cerebrovascular events (CVEs) within 30 days after transcatheter aortic valve implantation. TIA indicates transient ischemic attack.

Statistical Analysis

Categorical variables were expressed as percentages and continuous variables as mean (standard deviation) or median (25th–75 percentile) when not normally distributed. The normality distribution for continuous data was verified with the Shapiro-Wilk test. Comparison of numeric variables was performed by use of the 2-sided Student *t* test or Wilcoxon rank-sum test if necessary, and the χ^2 or Fischer exact test was used to compare qualitative variables. Variables with a value of $P<0.10$ in the univariate analysis were entered into a logistic regression analysis to determine the independent predictors of 30-day, acute, and subacute CVEs. Patients with acute (≤24 hours) CVEs or death were excluded from the analysis of the predictors of subacute CVEs. Univariate and multivariate competing-risk (mortality not related to CVE) regression analyses were done to determine the predictors of late CVEs (landmark analysis starting at 31 days, excluding patients with 30-day CVE or mortality) and cumulative CVEs (analysis starting at the time of the procedure). The association between CVE and mortality was assessed with the use of multivariate logistic regression (30-day mortality) or Cox proportional hazards (cumulative mortality) analyses including the variables with a value of $P<0.05$ in the univariate analysis. Freedom from CVE and mortality curves were calculated with the Kaplan-Meier method, and comparison between groups was obtained with the log-rank test. A value of $P<0.05$ was considered significant for all statistical tests. Analyses were done with the SAS statistical package, version 9.2 (SAS Institute Inc, Cary, NC).

Results

Baseline and procedural characteristics of the study population are shown in Table 1. Transfemoral approach was the access route in 726 patients (68.4%); transapical approach, in 322 patients (30.3%). At least 1 valve was implanted in 1040 patients (98%). The reasons that a valve could not be deployed are detailed in Table I in the online-only Data Supplement.

A total of 54 patients (5.1%) had a CVE within 30 days after the TAVI procedure, and the type of CVE was distributed as follows: stroke, 45 (4.2%); major stroke, 30 (2.8%); minor stroke, 15 (1.4%); and transient ischemic attack, 9 (0.8%). The stroke was of ischemic origin in all but 2 patients who experienced a hemorrhagic stroke confirmed by computed tomography. There were no significant differences in stroke rate between centers ($P=0.59$). The temporal distribution of CVEs is shown in Figure 2. A total of 29 of the 54 CVEs (54%) were acute (within 24 hours after TAVI) and 25 CVEs were subacute (1–30 days after TAVI). Details on antithrombotic treatment for all patients who suffered a CVE within 30 days are provided in Table II in the online-only Data Supplement.

Predictors of 30-Day (Acute and Subacute) CVEs

Baseline and procedural characteristics, grouped according to the occurrence of a CVE at 30 days, at ≤24 hours (acute), and at 1 to 30 days (subacute), are shown in Tables 1, 2, and 3, respectively. The results of univariate and multivariate analyses to determine the predictors of acute, subacute, and 30-day CVEs are shown in Table 4. New-onset atrial fibrillation (NOAF; odds ratio [OR], 2.27; 95% confidence interval [CI], 1.15–4.48; $P=0.018$) and balloon postdilation (OR, 1.94; 95% CI, 1.05–3.60; $P=0.034$) were the 2 independent predictors of CVEs within 30 days after the procedure (Table 4). The type of valve and approach did not affect the rate of CVE. Whereas balloon postdilation (OR, 2.46; 95% CI, 1.07–5.67; $P=0.034$) and valve embolization/dislodgment (OR, 4.36; 95% CI, 1.21–15.69; $P=0.024$) were the predictors of acute CVEs, NOAF was the only predictor of subacute CVEs after TAVI (OR, 2.76; 95% CI, 1.11–6.83; $P=0.028$).

Late (>30 Days) CVEs

The cumulative incidence of CVEs was 8.4% (n=89) at a median follow-up of 12 months (3–23 months). During the follow-up period, CVEs occurred in a total of 35 patients (3.3%; stroke, 2.1%), and 25 and 10 of them occurred at 1 to 12 and >12 months after TAVI, respectively. Stroke was diagnosed in 22 patients (16 ischemic, 6 hemorrhagic) and transient ischemic attack was diagnosed in 13 patients during the follow-up period. There were no differences in the rates of late stroke between participating centers ($P=0.92$). Details on antithrombotic treatment for all patients who suffered a late CVE are provided in Table III in the online-only Data Supplement. The Kaplan-Meier curves at the 1-year follow-up showing freedom from CVE, stroke, and major stroke are shown in Figure 3.

Baseline and procedural characteristics of the study population, grouped according to the occurrence of late CVEs and cumulative CVEs, are shown in Tables IV and V in the online-only Data Supplement. Results of the univariate and multivariate analyses to determine the predictors of late and cumulative CVEs are shown in Table 5.

Prognostic Value of 30-day CVEs

A total of 92 patients (8.7%) died within 30 days after the TAVI procedure, and 309 patients (29.1%) died during the follow-up period. The Kaplan-Meier survival curves up to the 1-year follow-up are shown in Figure 4. The occurrence of CVEs (16.7% versus 8.2%; $P=0.044$), stroke (20.0% versus 8.2%; $P=0.012$), and major stroke (30.0% versus 8.1%; $P=0.001$) was associated with a higher mortality rate at 30 days. The occurrence of 30-day stroke (33.1% versus 22.1%; $P=0.041$) or major stroke (41.6% versus 22.1%; $P=0.003$), but not CVEs (29.7% versus 22.2%; $P=0.152$), was associated with a higher 1-year mortality. The Kaplan-Meier survival curves at the 1-year follow-up according to the

Table 2. Baseline and Procedural Characteristics, According to the Occurrence of Acute (≤24 Hours) Cerebrovascular Events After Transcatheter Aortic Valve Implantation

Variables	Acute Cerebrovascular Event		
	Yes (n=29)	No (n=1032)	*P*
Baseline variables			
Age, y	82±6	81±8	0.269
Male sex, n (%)	12 (41.4)	526 (51.0)	0.308
BMI, kg/m^2	27.1±5.1	26.0±5.0	0.235
Diabetes mellitus, n (%)	10 (34.5)	302 (29.3)	0.543
Previous heart failure, n (%)	17 (58.6)	704 (68.2)	0.275
Hypertension, n (%)	21 (72.4)	769 (74.5)	0.798
NYHA functional class III–IV, n (%)	28 (96.6)	858 (83.1)	0.071
Chronic atrial fibrillation, n (%)	7 (24.1)	269 (26.1)	0.813
Coronary artery disease, n (%)	16 (55.2)	670 (64.9)	0.279
Previous myocardial infarction, n (%)	7 (24.1)	370 (35.9)	0.191
Prior CABG, n (%)	7 (24.1)	313 (30.3)	0.474
Cerebrovascular disease, n (%)	5 (17.2)	186 (18.0)	0.903
Peripheral vascular disease, n (%)	5 (17.2)	273 (26.5)	0.308
COPD, n (%)	11 (37.9)	299 (29.0)	0.295
Severely calcified aorta, n (%)	5 (17.2)	188 (18.2)	0.872
eGFR, mg/min	58.8±43.3	60.1±27.8	0.405
STS score, %	5.6 (3.9–9.3)	6.5 (4.3–9.7)	0.459
$CHADS_2$ score	2.9±1.1	2.9±1.2	0.900
Echocardiography data			
Mean aortic gradient, mm Hg	49±20	43±16	0.147
Aortic valve area, cm^2	0.59±0.15	0.66±0.19	0.086
LVEF <40%, n (%)	3 (10.3)	232 (22.5)	0.134
Complex aortic plaquest, n (%)	4 (25.0)	115 (17.1)	0.498
Periprocedural data, n (%)			
Learning curve*			0.354
First half	17 (3.2)	515 (96.8)	
Second half	12 (2.3)	517 (97.7)	
Approach			0.615
Transfemoral	23 (79.3)	703 (68.1)	
Transapical	6 (20.7)	316 (30.6)	
Subclavian	0	9 (0.9)	
Transaortic	0	4 (0.4)	
Prosthesis type			0.313
Cribier-Edwards	1 (3.4)	56 (5.4)	
Edwards Sapien	13 (44.8)	375 (36.3)	
Sapien XT	3 (10.3)	231 (22.4)	
CoreValve (second generation)	0	5 (0.5)	
CoreValve (third generation)	11 (37.9)	338 (32.8)	
St. Jude Portico	1 (3.4)	6 (0.6)	
Prosthesis size, mm			0.950
20	0	3 (0.3)	
23	10 (34.5)	295 (29.2)	
26	14 (48.3)	488 (48.3)	
29	5 (17.2)	223 (22.1)	
31	0	2 (0.2)	
Ratio of prosthesis size to annulus size	1.12±0.07	1.13±0.08	0.534
Balloon postdilation	10 (34.5)	179 (17.3)	0.017
Valve dislodgment/embolization	4 (13.8)	40 (3.9)	0.029
Need for a second valve	2 (6.9)	31 (3.0)	0.227
Need for hemodynamic support or severe maintained hypotension	3 (10.3)	51 (4.9)	0.181
Major vascular complication	3 (10.3)	97 (9.4)	0.749
New-onset atrial fibrillation	5 (17.2)	122 (11.8)	0.375
Antithrombotic treatment, n (%)			
Baseline			0.209
None	8 (27.6)	148 (14.3)	
Single antiplatelet therapy	10 (34.5)	421 (40.8)	
Dual antiplatelet therapy	4 (13.8)	159 (15.4)	
Anticoagulation therapy	2 (6.9)	185 (17.9)	
Single antiplatelet+ anticoagulation therapy	4 (13.8)	107 (10.4)	
Triple therapy	1 (3.4)	12 (1.2)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

occurrence of 30-day CVE, stroke, and major stroke are shown in Figure 4. The predictors of 30-day and cumulative mortality within the univariate and multivariate analyses are shown in Tables 6 and 7. Major stroke at 30 days was an independent predictor of mortality at 30 days (OR, 7.43; 95% CI, 2.45–22.53; P=0.001) and at follow-up (hazard ratio, 1.75; 95% CI, 1.01–3.04; P=0.043).

Discussion

In a large cohort of patients who underwent TAVI, the overall incidence of 30-day CVEs, regardless of valve type or access route, was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (≤24 hours) events were mechanical factors such us balloon postdilation of the valve prosthesis and the occurrence of valve dislodgment/embolization, whereas atrial arrhythmias (NOAF) determined mainly the events occurring in the subacute period (days 1–30) after the procedure. Late (>30 days) CVEs occurred in 3.3% of the patients (stroke, 2.1%) after a median follow-up of 12 months and were determined mainly by a history of chronic atrial fibrillation, peripheral vascular disease, and prior cerebrovascular disease. Major stroke at 30 days was associated with a higher mortality rate at 30 days and at follow-up.

Table 3. Baseline and Procedural Characteristics, According to the Occurrence of Subacute (1–30 Days) Cerebrovascular Events After Transcatheter Aortic Valve Implantation

Variables	Subacute Cerebrovascular Event		P
	Yes (n=25)	No (n=992)	
Baseline variables, n (%)			
Age, y	82±6	81±8	0.377
Male sex, n (%)	10 (40.0)	513 (51.7)	0.247
BMI, kg/m^2	26.2±4.3	26.0±5.0	0.882
Diabetes mellitus, n (%)	12 (48.0)	287 (28.9)	0.039
Previous heart failure, n (%)	15 (60.0)	680 (68.5)	0.364
Hypertension, n (%)	18 (72.0)	741 (74.7)	0.759
NYHA functional class III–IV, n (%)	21 (84.0)	826 (83.3)	0.923
Chronic atrial fibrillation, n (%)	8 (32.0)	257 (25.9)	0.495
Coronary artery disease, n (%)	16 (64.0)	650 (65.5)	0.874
Previous myocardial infarction, n (%)	9 (36.0)	359 (36.2)	0.978
Prior CABG, n (%)	7 (28.0)	305 (30.7)	0.769
Cerebrovascular disease, n (%)	4 (16.0)	181 (18.2)	0.763
Peripheral vascular disease, n (%)	4 (16.0)	264 (26.6)	0.234
COPD, n (%)	8 (32.0)	287 (28.9)	0.738
Severely calcified aorta, n (%)	9 (36.0)	175 (17.6)	0.032
eGFR, mg/min	62.2±40.1	60.3±26.7	0.737
STS score, %	6.5 (3.8–10.9)	6.5 (4.3–9.6)	0.986
$CHADS_2$ score	3.00±1.58	2.91±1.22	0.707
Echocardiography data			
Mean aortic gradient, mm Hg	42±15	43±17	0.734
Aortic valve area, cm^2	0.64±0.21	0.66±0.19	0.560
LVEF <40%, n (%)	5 (20.0)	223 (22.5)	0.753
Complex aortic plaques†, n (%)	2 (16.7)	113 (17.3)	0.956
Periprocedural data, n (%)			
Learning curve*			0.144
First half	16 (3.2)	488 (96.8)	
Second half	9 (1.8)	504 (98.2)	
Approach			0.957
Transfemoral	17 (68.0)	676 (68.1)	
Transapical	8 (32.0)	304 (30.6)	
Subclavian	0	8 (0.9)	
Transaortic	0	4 (0.4)	
Prosthesis type			0.447
Cribier-Edwards	2 (8.0)	54 (5.4)	
Edwards Sapien	7 (28.0)	363 (36.6)	
Sapien XT	3 (12.0)	228 (23.0)	
CoreValve (second generation)	0	5 (0.5)	
CoreValve (third generation)	13 (52.0)	318 (32.1)	
St. Jude Portico	0	6 (0.6)	
Prosthesis size, mm			0.879
20	0	3 (0.3)	
23	5 (20.0)	285 (29.3)	
26	14 (56.0)	470 (48.3)	
29	6 (24.0)	214 (22.0)	
31	0	2 (0.2)	
Ratio of prosthesis size to annulus size	1.15±0.06	1.13±0.08	0.406
Balloon postdilation	6 (24.0)	172 (17.3)	0.421
Valve dislodgment/ embolization	0	38 (3.8)	0.381
Need for a second valve	0	30 (3.0)	0.469
Need for hemodynamic support or severe maintained hypotension	1 (4.0)	44 (4.5)	1.000
Major vascular complications	0	93 (9.4)	0.158
New-onset atrial fibrillation	7 (28.0)	115 (11.6)	0.023
Antithrombotic treatment, n (%)			
Baseline			0.309
None	5 (20.0)	139 (14.0)	
Single antiplatelet therapy	12 (48.0)	402 (40.5)	
Dual antiplatelet therapy	1 (4.0)	157 (15.8)	
Anticoagulation therapy	5 (20.0)	177 (17.8)	
Single antiplatelet+ anticoagulation therapy	1 (4.0)	106 (10.7)	
Triple therapy	1 (4.0)	11 (1.1)	
Discharge			0.210
None	0 (0)	17 (1.8)	
Single antiplatelet therapy	0 (0)	83 (8.9)	
Dual antiplatelet therapy	9 (40.9)	513 (54.8)	
Anticoagulation therapy	2 (9.1)	49 (5.2)	
Single antiplatelet+ anticoagulation therapy	9 (40.9)	237 (25.3)	
Triple therapy	2 (9.1)	37 (4.0)	
30-d Follow-up			0.162
None	0 (0)	10 (1.2)	
Single antiplatelet therapy	0 (0)	74 (8.7)	
Dual antiplatelet therapy	9 (40.9)	470 (55.2)	
Anticoagulation therapy	3 (13.6)	50 (5.9)	
Single antiplatelet+ anticoagulation therapy	8 (36.4)	217 (25.5)	
Triple therapy	2 (9.1)	30 (3.5)	

BMI indicates body mass index; NYHA, New York Heart Association; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and LVEF, left ventricular ejection fraction. Data are presented as mean±SD or median (interquartile range) as appropriate.

*First versus second cohort of patients in each participating center.

†Data available in 689 patients.

CVEs at 30 Days

The 5.1% rate of CVEs at 30 days, with a 4.2% stroke rate, is consistent with the rates reported in registries (stroke, ≈3.5%, ranging from 1.7%–4.1%),[3–8] in a recent meta-analysis (3.3±1.8%),[9] and in the PARTNER trial (cohort A: 5.5%; stroke, 4.7%; cohort B: 6.7%; stroke, 6.7%).[10,11] In addition, some preliminary data suggested that about half of the CVEs occur during or very early after the procedure (≤24

Table 4. Univariate and Multivariate Predictors of Cerebrovascular Events Within 30 Days After Transcatheter Aortic Valve Implantation

	Univariate Analysis		Multivariate Analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Predictors of 30-d cerebrovascular events				
New-onset atrial fibrillation	2.21 (1.13–4.33)	0.017	2.27 (1.15–4.48)	0.018
Balloon postdilation	1.95 (1.06–3.58)	0.020	1.94 (1.05–3.60)	0.034
Diabetes mellitus	1.70 (0.97–2.97)	0.061	1.76 (0.97–3.10)	0.055
Learning curve (second half)	0.62 (0.36–1.09)	0.098	0.62 (0.35–1.10)	0.105
Predictors of acute (≤24 h) cerebrovascular events				
Balloon postdilation	2.51 (1.15–5.49)	0.017	2.46 (1.07–5.67)	0.034
Valve dislodgment/embolization	3.97 (1.32–11.94)	0.029	4.36 (1.21–15.69)	0.024
Aortic valve area (per 0.1-cm^2 decrease)	1.21 (0.97–1.53)	0.086	1.22 (0.96–1.53)	0.097
NYHA functional class III–IV	5.68 (0.77–42.01)	0.071	5.06 (0.68–37.77)	0.114
Predictors of subacute (1-d–30-d) cerebrovascular events				
New-onset atrial fibrillation	2.96 (1.21–7.25)	0.023	2.76 (1.11–6.83)	0.028
Severely calcified aorta	2.59 (1.13–5.97)	0.032	2.28 (0.98–5.30)	0.056
Diabetes mellitus	2.27 (1.02–5.03)	0.039	2.17 (0.97–4.84)	0.060

OR indicates odds ratio; CI, confidence interval; and NYHA, New York Heart Association.

hours),[10,18,25] and our analysis of a large number of patients including different valve types and approaches confirms this high risk of CVEs in the very early period after TAVI.

The present study shows that both procedural mechanical factors such as balloon postdilation and atrial arrhythmias were the main predictors of CVEs within 30 days after the TAVI procedure, but the temporal trends for the increased embolic risk associated with these 2 factors were very different. While balloon postdilation determined a higher risk of acute (≤24 hours) events, the occurrence of atrial arrhythmias was associated with a higher risk of subacute (days 1–30) events. Transcranial Doppler studies have shown that most cerebral high-intensity transient signals occur during valve positioning and implantation,[12–15] suggesting that the mechanical interaction between the transcatheter valve and the calcified native aortic valve plays a major role in periprocedural cerebral emboli. Miller et al[16] showed that patients with smaller valve areas had a higher risk of CVEs in the early period after TAVI (up to 7 days after the procedure), which indirectly supports the role of the calcified native valve in postprocedural CVEs, especially in view of the good correlation between the degree of valve calcification and aortic stenosis severity.[26] The presence of a smaller valve area showed a clear tendency toward a higher rate of acute events in our study, although this variable was not found to be an independent predictor of CVEs in the multivariable analysis. Balloon postdilation is used in about one fourth of the patients after valve prosthesis implantation, with the objective of reducing residual aortic regurgitation secondary to paravalvular leaks.[27–29] Preliminary data suggested an increase in CVEs with balloon postdilation,[17] and the results of the present study confirm that the further stretching of the calcified native valve during balloon postdilation is independently associated with a >2-fold risk of CVEs immediately or within the first few hours after the procedure. Balloon postdilation increases the interaction between the stent frame of the valve prosthesis and the native aortic valve, which might indeed favor the dislodgment of calcific particles from the native valve. The results of our study suggest that balloon postdilation should probably be limited to those patients with a more significant paravalvular leak. The study also highlights the importance of an appropriate sizing of the aortic annulus to avoid the implantation of undersized valves requiring further balloon postdilation and the development of valve prostheses with antiparavalvular leak properties. Finally, the use of embolic protection devices may be of particular importance in patients requiring balloon postdilation.[30–32]

Valve dislodgment and/or embolization occurred in up to 4.1% of the patients in this study. Valve dislodgment has been described mostly for the self-expandable CoreValve system; it is usually managed by pulling back the partially deployed valve through the aortic arch and descending aorta up to the 18F iliofemoral sheath.[33] Valve prosthesis embolization occurs mainly toward the ascending aorta; the valve prosthesis is usually removed up to the aortic arch or descending aorta with the use of an inflated balloon within the valve or by snaring the prosthesis stent frame.[34,35] All these maneuvers are associated with significant mechanical friction between the prosthesis frame and the aortic wall and are potentially highly thromboembolic. This study shows, for the first time, that this complication is associated with a high risk of periprocedural acute CVEs and highlights the importance of accurate valve positioning and implantation to avoid this complication. In addition, the development of valve prostheses that can be fully recaptured in case of valve malpositioning may contribute to reducing this complication.

NOAF is a well-known complication associated with cardiac surgery, and its occurrence has been associated with

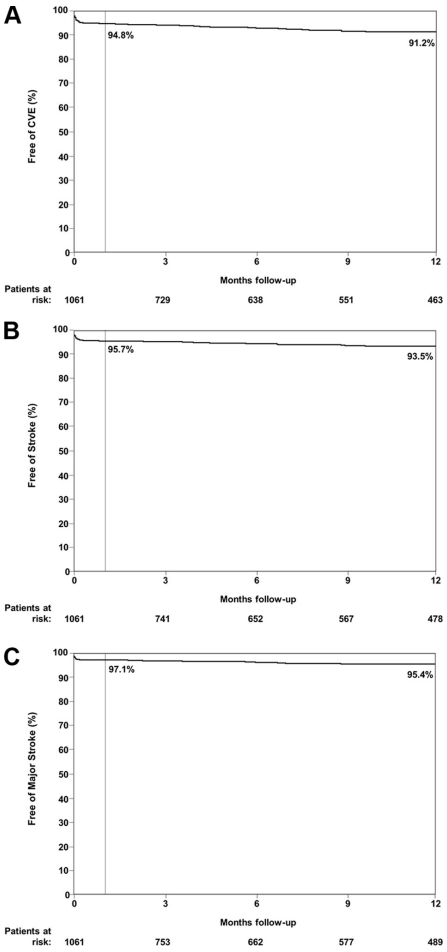


Figure 3. Kaplan-Meier survival curves up to 1 year of follow-up showing the percentage of patients free of cerebrovascular events (CVEs; **A**), stroke (**B**), and major stroke (**C**) after transcatheter aortic valve implantation.

a higher rate of periprocedural CVEs and cardiac mortality.[36] NOAF occurred in 12% of the patients in the present study (18% after exclusion of those patients with prior chronic atrial fibrillation), which is similar to the 15% rate observed in the PARTNER trial among those patients with no prior history of AF.[11] Two recent studies in the TAVI field including a relatively low number of patients suggested an increased risk of CVEs when NOAF occurs as a complication of the TAVI procedure.[19,20] The results of the present study confirm these preliminary findings in a large cohort of patients and using an appropriate multivariate model for determining predictive factors for CVEs. Of note, this complication was found to be the one mainly responsible for those CVEs occurring in the subacute phase (1–30 days) of the postprocedural period, suggesting that improvements in both the prevention of atrial arrhythmias and antithrombotic treatment after the procedures should play a role in the reduction of the 30-day CVE rate associated with TAVI.

Previous studies with magnetic resonance imaging or transcranial Doppler have shown a similar incidence of silent new ischemic lesions or transient signals, respectively, between transfemoral or transapical approaches, and clinical studies have failed to show any significant differences in CVE rate between the 2 approaches.[2–11] The results of our study are consistent with these previous data and indirectly support the interaction between valve prosthesis and the native aortic valve as the main mechanism of CVE during TAVI procedures. Also in accordance with previous studies,[2–11] similar rates of CVEs were observed with the use of balloon-expandable and self-expandable transcatheter valves.

Late CVEs

The incidence of late (>30-day) CVEs, stroke, and major stroke was 3.3%, 2.1%, and 1.7%, respectively. This is similar to the late CVE and stroke rates reported in the PARTNER trial.[10,11] Miller et al[16] showed that patients with prior stroke and "nontransfemoral candidates" had a higher rate of late CVEs after TAVI. The present study shows, for the first time, that chronic atrial fibrillation was the main predictor of late CVEs, in addition to both peripheral vascular disease and prior cerebrovascular disease. Therefore, the factors associated with these late events reflect the background risks of this population and make it highly unlikely that late CVEs after TAVI could be related to the valve prosthesis or the procedure per se. In accordance with these results, TAVI was not found to be a significant risk factor for late neurological events in the PARTNER trial.[16] The population undergoing TAVI nowadays consists of patients of advanced age with several comorbidities, which increases the risk for CVEs in the follow-up period. The stroke rate increases with each decade of life, reaching a rate of ≈1.9%/y in patients ≥85 years of age, comparable to our late stroke rate of 2.1%, in a population with a lower risk profile than TAVI candidates.[37] More than 25% of our study population had chronic atrial fibrillation, which is a known risk factor for future CVEs even with anticoagulant therapy, with an incidence of 2.4%/y in patients on warfarin treatment.[38] Indeed, the median $CHADS_2$ score of our study population was ≈3, which emphasizes the importance of an appropriate anticoagulation treatment in such patients. However, up to 6 patients with late CVEs presented with hemorrhagic stroke (27% of late strokes), also highlighting the difficult equilibrium between ischemic and bleeding events in this very old and high-risk population.

Prognosis of CVE

Several studies have demonstrated the poorer short- and long-term outcomes of patients who suffer a stroke after aortic valve replacement.[22,39] Although data on CVEs and outcomes in TAVI patients are very limited, in a substudy of the PARTNER trial,[16] mortality in TAVI and aortic valve

Table 5. Univariate and Multivariate Predictors of Late (>30-Day) and Cumulative Cerebrovascular Events After Transcatheter Aortic Valve Implantation

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Predictors of late (>30-d) cerebrovascular events				
Chronic atrial fibrillation	2.83 (1.45–5.50)	0.002	2.84 (1.46–5.53)	0.002
Peripheral vascular disease	2.19 (1.12–4.27)	0.022	2.02 (1.02–3.97)	0.043
Cerebrovascular disease	2.35 (1.17–4.73)	0.016	2.04 (1.01–4.15)	0.047
Antithrombotic treatment at hospital discharge*	2.57 (1.32–5.00)	0.005	1.73 (0.78–3.81)	0.172
Predictors of cumulative cerebrovascular events				
Age, y (per 1-y increase)	1.03 (1.00–1.07)	0.032	1.03 (1.01–1.06)	0.043
Chronic atrial fibrillation	1.62 (1.05–2.51)	0.030	1.91 (1.19–3.06)	0.007
Balloon postdilation	1.74 (1.09–2.78)	0.020	1.88 (1.17–3.00)	0.008
New-onset atrial fibrillation	1.93 (1.15–3.24)	0.013	2.53 (1.45–4.43)	0.001
Antithrombotic treatment at hospital discharge*	1.70 (1.12–2.58)	0.013	1.22 (0.74–2.01)	0.429

HR indicates hazard ratio; CI, confidence interval.
*Anticoagulation therapy (with or without antiplatelet therapy).

replacement patients was higher than expected after a CVE. More recently, Stortecky et al[18] found a higher risk of 30-day mortality in patients who suffered a CVE. Tamburino et al[7] found periprocedural stroke to be a predictor of increased mortality in 663 patients treated with the CoreValve system. In accordance with these data, our study also points to the negative impact of this complication in 30-day and late outcomes after TAVI. In a further step, the results of the present study also show that the impact of CVEs on mortality was determined mainly by the severity of the neurological

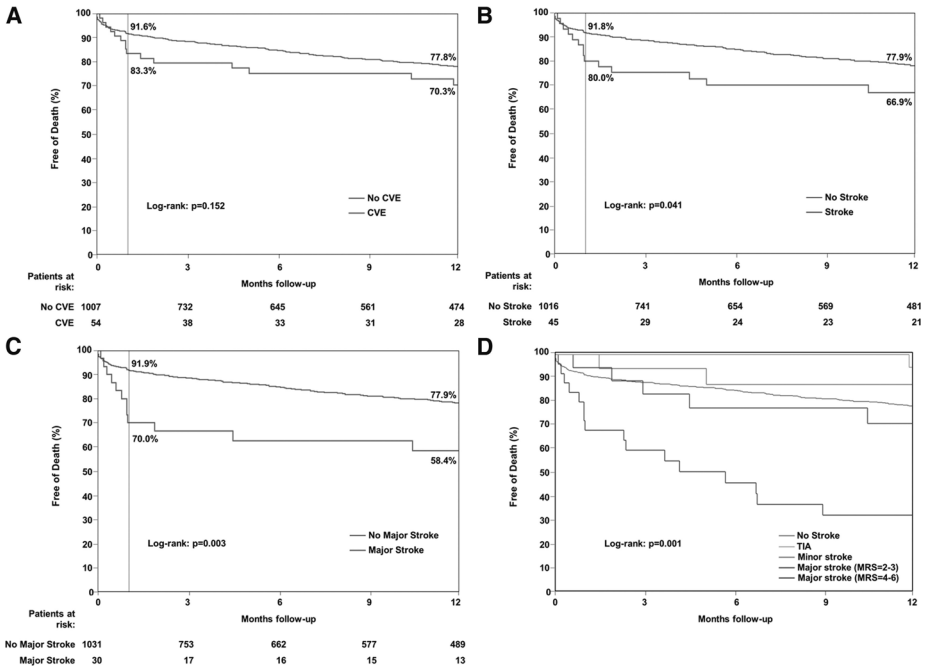


Figure 4. Kaplan-Meier survival curves up to 1 year of follow-up showing the percentage of patients free of death according to the occurrence of early (<30 days) cerebrovascular events (CVEs; **A**), stroke (**B**), major stroke (**C**), and severity of the CVE as assessed by the Modified Rankin scale (**D**) after transcatheter aortic valve implantation.

Table 6. Univariate and Multivariate Predictors of 30-Day Mortality After Transcatheter Aortic Valve Implantation

	Univariate Analysis			Multivariate Analysis		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
eGFR <60 mL/min	1.92	1.20–3.08	0.007	1.03	0.52–2.03	0.938
STS (each increase in 1%)	2.31	1.67–3.18	0.001	1.66	0.96–2.87	0.070
Mitral regurgitation (baseline) ≥3	2.03	1.28–3.22	0.002	1.76	0.89–3.47	0.103
Learning curve (second half)	0.43	0.27–0.68	0.001	0.72	0.36–1.45	0.361
Device success	0.34	0.21–0.56	0.001	0.51	0.23–1.12	0.093
Need hemodynamic support or severe maintained hypotension	11.0	6.09–19.84	0.001	4.45	1.73–11.47	0.002
Life-threatening bleeding	7.87	4.65–13.34	0.001	7.15	3.37–15.20	0.001
Major stroke at 30 d	4.89	2.17–11.03	0.001	7.43	2.45–22.53	0.001
Aortic regurgitation (post-TAVI) ≥2	2.28	1.27–4.07	0.004	2.33	1.18–4.58	0.015

OR indicates odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

event, and only events leaving permanent deficits (major stroke) were associated with a significantly increased risk of early and late mortality after TAVI, even after adjustment for other major procedural complications and baseline clinical characteristics. Furthermore, this finding highlights the major importance of understanding the mechanisms associated with CVEs for implementing the appropriate measures to reduce its occurrence.

Limitations

This study has several limitations. Although the data were prospectively collected in each participating center, there was no prespecified case report form or event adjudication committee for this study. No systematic neurological evaluation of the patients by a neurology specialist was performed before and after the procedure. However, although this might have led to some minor events being missed, it seems unlikely that this would have been associated with significant changes in the rates of major stroke. The evaluation of complex aortic atheroma plaques by transesophageal echocardiography was available in about two thirds of the patients, and this might have precluded an appropriate evaluation of the role of this important factor in the occurrence of CVEs.

Conclusions

TAVI was associated with an increased risk of early CVEs after the procedure, with the highest risk occurring immediately after or within the first few hours after TAVI and extending throughout several days after the procedure, with those events leaving permanent neurological defects (major

Table 7. Univariate and Multivariate Predictors of Cumulative Mortality After Transcatheter Aortic Valve Implantation

	Univariable			Multivariable		
Variable	HR	95% CI	*P*	HR	95% CI	*P*
Sex (male)	1.47	1.17–1.84	0.001	1.57	1.22–2.02	0.001
Chronic AF	1.72	1.36–2.17	0.001	1.62	1.27–2.08	0.001
Previous MI	1.28	1.02–1.61	0.031	1.08	0.85–1.39	0.519
Peripheral vascular disease	1.41	1.11–1.80	0.004	1.06	0.78–1.45	0.717
COPD	1.40	1.11–1.76	0.005	1.33	1.03–1.71	0.028
eGFR <60 mL/min	1.51	1.19–1.90	0.001	1.27	0.99–1.64	0.062
LVEF <40%	1.49	1.16–1.91	0.002	1.16	0.88–1.53	0.288
Pulmonary hypertension	1.69	1.25–2.28	0.001	1.34	0.98–1.84	0.067
STS (each increase in 1%)	1.95	1.66–2.30	0.001	1.76	1.44–2.16	0.001
Nontransfemoral approach	1.37	1.09–1.73	0.007	1.12	0.83–1.51	0.467
Need hemodynamic support or severe maintained hypotension	3.52	2.44–5.09	0.001	2.66	1.72–4.10	0.001
Life-threatening bleeding	2.39	1.75–3.26	0.001	2.18	1.54–3.08	0.001
Major stroke at 30 d	2.07	1.23–3.48	0.006	1.75	1.01–3.04	0.043

HR indicates hazard ratio; CI, confidence interval; AF, atrial fibrillation; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and STS, Society of Thoracic Surgeons.

stroke) being associated with much poorer short-term and midterm outcomes. Mechanical factors such as further stretching of the valve prosthesis with balloon postdilation or valve dislodgment/embolization determined a higher risk of acute (≤24 hours) CVEs and highlight the importance of further evaluating the potential usefulness of embolic protection devices during TAVI procedures. The occurrence of atrial arrhythmias increased the risk of subacute (1–30 days) CVEs and suggests that efforts to reduce these events should probably focus on both determining the most appropriate antithrombotic treatment after TAVI and establishing preventive therapies to reduce the occurrence of new episodes of AF. Finally, late (>30 days) events were associated mainly with an increased atherosclerotic burden and chronic atrial arrhythmias, both well-known risk factors of CVEs. These results providing important insight into the pathophysiology and prognostic value of CVEs after TAVI procedures should help to determine the most appropriate therapeutic measures to reduce the high incidence of CVEs associated with TAVI.

Acknowledgments

We would like to thank Melanie Côté, MSc, and Serge Simard, MSc, from the Quebec Heart and Lung Institute for their help in the preparation of figures and statistical analyses, respectively.

Sources of Funding

Dr Nombela-Franco received funding via a research grant from the Fundación Alfonso Martín Escudero (Spain). Drs Toggweiler and Binder are supported by a grant from the Swiss National Foundation.

Disclosures

Drs Webb, Cheung, and Rodés-Cabau are consultants for Edwards Lifesciences and St. Jude Medical. Dr de Jaegere is a proctor for Medtronic. Drs Dumont and Binder are consultants for Edwards Lifesciences. Dr DeLarochellière is a consultant for St. Jude Medical. The other authors report no conflicts.

References

1. Rodés-Cabau J. Transcatheter aortic valve implantation: current and future approaches. *Nat Rev Cardiol*. 2011;9:15–29.
2. Hynes GB, Rodés-Cabau J. Transcatheter aortic valve implantation and cerebrovascular events: the current state of the art. *Ann N Y Acad Sci*. 2012;1254:151–163.
3. Thomas M, Schymik G, Walther T, Himbert D, Lefèvre T, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O. Thirty-day results of the SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) Registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. *Circulation*. 2010; 122:62–69.
4. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080–1090.
5. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Hauptmann KE, Richardt G, Figulla HR, Senges J; German Transcatheter Aortic Valve Interventions-Registry Investigators. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. *Eur Heart J*. 2010;32:198–204.
6. Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med*. 2012;366:1705–1715.
7. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. *Circulation*. 2011;123:229–308.
8. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58:2130–2138.
9. Eggebrecht H, Schmermund A, Voigtländer T, Kahlert P, Erbel R, Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. *EuroIntervention*. 2012;8: 129–38.
10. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363: 1597–1607.
11. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187–2198.
12. Drews T, Pasic M, Buz S, Unbehaun A, Dreysse S, Kukucka M, Mladenow A, Hetzer R. Transcranial Doppler sound detection of cerebral microembolism during transapical aortic valve implantation. *Thorac Cardiovasc Surg*. 2011;59:237–242.
13. Szeto WY, Augoustides JG, Desai ND, Moeller P, McGarvey ML, Walsh E, Bannan A, Herrmann HC, Bavaria JE. Cerebral embolic exposure during transfemoral and transapical transcatheter aortic valve replacement. *J Card Surg*. 2011;26:348–354.
14. Erdoes G, Basciani R, Huber C, Stortecky S, Wenaweser P, Windecker S, Carrel T, Eberle B. Transcranial Doppler-detected cerebral embolic load during transcatheter aortic valve implantation. *Eur J Cardiothorac Surg*. 2012;41:778–784.
15. Kahlert P, Al-Rashid F, Doettger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R, Eggebrecht H. Cerebral embolization during transcatheter aortic valve implantation: a transcranial Doppler study. *Circulation*. 2012;126:1245–1255.
16. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, Rajeswaran J, Anderson WN, Moses JW, Tuzcu EM, Webb JG, Leon MB, Smith CR. Occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012;143:832–843.
17. Nombela-Franco L, Rodés-Cabau J, DeLarochellière R, Larose E, Doyle D, Villeneuve J, Bergeron S, Bernier M, Amat-Santos IJ, Mok M, Urena M, Rheault M, Dumesnil J, Côté M, Pibarot P, Dumont E. Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. *JACC Cardiovasc Interv*. 2012;5:499–512.
18. Stortecky S, Windecker S, Pilgrim T, Heg D, Buellesfeld L, Khattab AA, Huber C, Gloekler S, Nietlispach F, Mattle H, Jüni P, Wenaweser P. Cerebrovascular accidents complicating transcatheter aortic valve implantation: frequency, timing and impact on outcomes. *EuroIntervention*. 2012;8:62–70.
19. Amat-Santos IJ, Rodés-Cabau J, Urena M, DeLarochellière R, Doyle D, Bagur R, Villeneuve J, Côté M, Nombela-Franco L, Philippon F, Pibarot P, Dumont E. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:178–188.
20. Nuis RJ, Van Mieghem NM, Schultz CJ, Moelker A, van der Boon RM, 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.
21. Salazar JD, Wityk RJ, Grega MA, Borowicz LM, Doty JR, Petrofski JA, Baumgartner WA. Stroke after cardiac surgery: short- and long-term outcomes. *Ann Thorac Surg*. 2001;72:1195–1201.
22. Filsoufi F, Rahmanian PB, Castillo JG, Bronster D, Adams DH. Incidence, imaging analysis, and early and late outcomes of stroke after cardiac valve operation. *Am J Cardiol*. 2008;101:1472–1478.
23. Kronzon I, Tunick PA. Aortic atherosclerotic disease and stroke. *Circulation.* 2006;114:63–75.
24. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57: 253–269.
25. Tay EL, Gurvitch R, Wijesinghe N, Nielispach F, Wood D, Cheung A, Ye J, Lichtenstein SV, Carere R, Thompson C, Webb JG. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2011;4:1290–1297.
26. Messika-Zeitoun D, Aubry MC, Detaint D, Bielak LF, Peyser PA, Sheedy PF, Turner ST, Breen JF, Scott C, Tajik AJ, Enriquez-Sarano M. Evaluation and clinical implications of aortic valve calcification measured by electron-beam computed tomography. *Circulation*. 2004;110:356–362.
27. Takagi K, Latib A, Al-Lamee R, Mussardo M, Montorfano M, Maisano F, Godino C, Chieffo A, Alfieri O, Colombo A. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. *Catheter Cardiovasc Interv*. 2011;78:432–443.
28. Schultz C, Rossi A, van Mieghem N, van der Boon R, Papadopoulou SL, van Domburg R, Moelker A, Mollet N, Krestin G, van Geuns RJ, 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*. 2011;7:564–572.
29. Kempfert J, Rastan A, Holzhey D, Linke A, Schuler G, van Linden A, Blumenstein J, Mohr FW, Walther T. Transapical aortic valve implantation: analysis of risk factors and learning experience in 299 patients. *Circulation*. 2011;124:S124–S129.
30. Nietlispach F, Wijesinghe N, Gurvitch R, Tay E, Carpenter JP, Burns C, Wood DA, Webb JG. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Interv*. 2010;3:1133–1138.
31. Onsea K, Agostoni P, Samim M, Voskuil M, Kluin J, Budde R, Hendrikse J, Ramjankhan F, van Klarenbosch J, Doesburg P, Sieswerda G, Stella P. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. *EuroIntervention.* 2012;15:8:51–56.
32. Naber CK, Ghanem A, Abizaid AA, Wolf A, Sinning JM, Werner N, Nickenig G, Schmitz T, Grube E. First-in-man use of a novel embolic protection device for patients undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2012;15:43–50.
33. Van Mieghem N, Schultz CJ, van der Boon R, Nuis RJ, Tzikas A, Geleijnse ML, Domburg RT, Serruys PW, de Jaegere P. Incidence, timing and predictors of valve dislodgment during TAVI with the Medtronic CoreValve system. *Catheter Cardiovasc Interv*. 2012;79:726–732.
34. Ali AM, Altwegg L, Horlick EM, Feindel C, Thompson CR, Cheung A, Carere RG, Humphries K, Ye J, Masson JB, Webb JG. Prevention and management of transcatheter balloon-expandable aortic valve malposition. *Catheter Cardiovasc Interv*. 2008;72:573–578.
35. Sarkar K, Ussia GP, Tamburino C. Core Valve embolization: technical challenges and management. *Catheter Cardiovasc Interv*. 2012;79: 777–782.
36. Kaireviciute D, Aidietiset A, Lip GY. Atrial fibrillation following cardiac surgery: clinical features and preventive strategies. *Eur Heart J*. 2009; 30:410–425.
37. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham Heart Study. *Stroke*. 2009;40:1032–1037.
38. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.
39. Melby SJ, Zierer A, Kaiser SP, Guthrie TJ, Keune JD, Schuessler RB, Pasque MK, Lawton JS, Moazami N, Moon MR, Damiano RJ Jr. Aortic valve replacement in octogenarians: risk factors for early and late mortality. *Ann Thorac Surg*. 2007;83:1651–1656.

CLINICAL PERSPECTIVE

Transcatheter aortic valve implantation has been associated with a higher rate of cerebrovascular events (CVEs) compared with medical treatment or surgical aortic valve replacement. This multicenter study evaluated in a large cohort of consecutive patients (n=1061) the timing, predictors, and clinical impact of CVEs after transcatheter aortic valve implantation. The incidence of 30-day CVEs was 5.1% (stroke, 4.2%), with about half of these events occurring immediately or within the first few hours after the procedure. The predictors of acute (≤24 hours) CVEs were mechanical factors such as further stretching of the valve prosthesis with balloon postdilation (odds ratio, 2.46; $P=0.034$) and valve dislodgment/embolization (odds ratio, 4.36; $P=0.024$), whereas subacute (1–30 days) CVEs were determined mainly by the occurrence of atrial arrhythmias (new-onset atrial fibrillation; odds ratio, 2.76; $P=0.028$). There were no differences in 30-day CVE rate between different types of valves (balloon expandable, self-expandable) or access routes (transfemoral, transapical). The rate of late (<30 days) CVEs was 3.3% (stroke, 2.1%) at a median follow-up of 12 months (3–23 months). The predictors of late CVEs were chronic atrial fibrillation (hazard ratio, 2.84; $P=0.002$), peripheral vascular disease (hazard ratio, 2.02; $P=0.043$), and prior cerebrovascular disease (hazard ratio, 2.04; $P=0.047$). The impact of CVEs on mortality was determined mainly by the severity of the event, and only the occurrence of major stroke was independently associated with an increased 30-day (hazard ratio, 7.43; $P=0.001$) and late cumulative (hazard ratio, 1.75; $P=0.043$) mortality. These results providing important insight into the pathophysiology and prognosis value of CVEs after transcatheter aortic valve implantation procedures should help to determine the most appropriate therapeutic measures to reduce the high incidence of CVEs associated with transcatheter aortic valve implantation.

PART 4

FREQUENCY AND PATHOPHYSIOLOGY OF ACUTE KIDNEY INJURY

CHAPTER 10

Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation

Frequency, Determinants, and Prognostic Effects of Acute Kidney Injury and Red Blood Cell Transfusion in Patients Undergoing Transcatheter Aortic Valve Implantation

Rutger-Jan M. Nuis,[1] MSc, Nicolas M. Van Mieghem,[1] MD, Apostolos Tzikas,[1] MD, Nicolo Piazza,[1] MD, Amber M. Otten,[1] MSc, Jin Cheng,[1] MD, Ron T. van Domburg,[1] PhD, Michiel Betjes,[2] MD, PhD, Patrick W. Serruys,[1] MD, PhD, and Peter P.T. de Jaegere,[1*] MD, PhD

Objectives: To determine the frequency and independent predictors of acute kidney injury (AKI) in addition to the prognostic implications of both AKI and periprocedural red blood cell (RBC) transfusions on 30 day and cumulative late mortality in patients undergoing transcatheter aortic valve implantation (TAVI). Background: RBC transfusions have been reported to predict AKI following TAVI. Data on the prognostic implications of both factors, however, are lacking. Methods: 126 consecutive patients underwent TAVI with the Medtronic CoreValve Revalving System. AKI was defined according to the valve academic research consortium definitions as an absolute increase in serum creatinine $\geq$0.3 mg dL^{-1} ($\geq$26.4 μmol L^{-1}) or a percentage increase $\geq$50% within 72 hr following TAVI. Results: Five patients on chronic haemodialysis and three intraprocedural deaths were excluded, leading to a final study population of 118 patients. AKI occurred in 19% of the patients necessitating temporary haemodialysis in 2%. Independent predictors of AKI included: previous myocardial infarction (OR: 5.72; 95% CI: 1.64–19.94), periprocedural (<24 hr) RBC transfusions (OR: 1.29; 95% CI: 1.01–1.70), postprocedural (<72 hr) leucocyte count (OR: 1.18; 95% CI: 1.02–1.37), and logistic EuroSCORE (OR: 1.08; 95% CI: 1.01–1.14). In patients with AKI, 30-day mortality was 23% and cumulative late mortality (median: 13 months) was 55%. AKI (OR: 5.47; 95% CI: 1.23–24.21) and postprocedural leucocyte count (OR: 1.20; 95% CI: 1.03–1.38) were independent predictors of 30-day mortality while AKI (HR: 2.79; 95% CI: 1.36–5.71) was the only independent predictor of late mortality. Conclusions: AKI following TAVI occurred in 19% of the patients. RBC transfusion was found to be an independent predictor of AKI, which in turn predicted both 30-day and cumulative late mortality.

Key words: aortic valve replacement; percutaneous heart valve; acute renal failure; prognosis

INTRODUCTION

Surgical aortic valve replacement (AVR) with cardiopulmonary bypass is the standard treatment for patients with severe aortic stenosis and is associated with a low morbidity and mortality rate in selected patients [1]. Yet, acute kidney injury (AKI) following cardiac surgery is reported to occur in 4–30% of the patients [2,3] and is associated with an increased mortality that is proportional to the severity of AKI [4,5]. In addition, a number of studies found that small increments in serum creatinine also adversely affect mortality [2,3,6,7].

Transcatheter aortic valve implantation (TAVI) is a less invasive technique that is performed on the beating heart without the need of extracorporeal support and may, therefore, be associated with a lower incidence of

[1]Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands
[2]Department of Nephrology, Erasmus Medical Center, Rotterdam, The Netherlands

Conflict of interest: N. Piazza is a consultant to Medtronic; P. de Jaegere is a proctor for Medtronic.

*Correspondence to: Peter P.T. de Jaegere, MD, PhD, Thoraxcenter, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands. E-mail: p.dejaegere@erasmusmc.nl

Received 20 August 2010; Revision accepted 14 October 2010

DOI 10.1002/ccd.22874
Published online 16 March 2011 in Wiley Online Library (wileyonlinelibrary.com)

AKI. Yet, TAVI is currently performed in elderly patients or patients deemed too high a risk for AVR because of severe comorbidities. They often have impaired renal function and are, therefore, at increased risk for AKI also after TAVI due to the haemodynamic changes during the procedure and the use of contrast agents. The risk of AKI has been shown to be independently associated with periprocedural red blood cell (RBC) transfusions during cardiac surgery [8,9] and TAVI [10,11]. Both may synergistically affect mortality. The objectives of this study were to determine the incidence and predictive factors of AKI following TAVI in addition to the prognostic effects of RBC transfusions and AKI on 30-day and cumulative late mortality.

MATERIALS AND METHODS

Patients and Procedure

A total of 126 patients with aortic stenosis underwent TAVI with the Medtronic CoreValve Revalving System (CRS) between November 2005 and April 2010. Patients were accepted for TAVI on the basis of an agreement between a cardiologist and a cardiac surgeon during the heartteam meeting. In accordance with the institution policy, every patient gave written informed consent for treatment and all clinical data were collected in the context of a structured follow-up to which every patient treated in our department is subjected in accordance with IRB approval.

Criteria for the implantation of the Medtronic CRS have been described elsewhere [12]. Details of the device and the procedure have been previously published [13]. All patients underwent a standard preoperative coronary angiography at a median (IQR) of 60 (38–96) days before TAVI. In 83 patients (70%), multi-sliced computed tomography was performed at a median (IQR) of 58 (22–85) days before the procedure during which a contrast bolus (50–60 mL Visipaque® 320 mg mL^{-1}, GE Health Care, Eindhoven, The Netherlands) was injected in an antecubital vein at a flow rate of 5.0 mL sec^{-1} followed by a second contrast bolus of 30–40 mL at 3.0 mL sec^{-1} up to a total of 80 mL. According to the in-hospital protocol, all patients with a glomerular filtration rate (GFR) <45 mL min^{-1} in the absence of diabetes or GFR <60 mL min^{-1} in the presence of diabetes and/or two other risk factors for impaired renal function after contrast agents (e.g. age >75, heart failure) received prehydration (NaCl 0.9%, 12–16 mL kg^{-1} 4–6 hr before and after TAVI).

Definitions and Collection of Data

Predefined baseline characteristics, medication and technical measurements (electrocardiography, echo-Doppler) were prospectively collected during the outpatient clinic visit prior to the procedure. Blood samples for haematology and chemistry were taken 1 day before TAVI and daily up to 72-hr post-treatment. Haematological variables included the nadir haemoglobin concentration, nadir platelet count, maximal leucocyte count and maximal serum creatinine (SCr). Creatinine-based equations for estimation of GFR were applied to identify patients with impaired renal function and to classify them in chronic kidney disease stage I, II, and III, defined as a preprocedural GFR of >90, 60–89, and <60 mL/min/1.73m^2, respectively. The simplified modification of diet in renal disease formula [14] was used to estimate GFR, which is normalized to 1.73 m^2 body surface area and adjusted for sex, age, race, and SCr.

AKI was defined according to the valve academic research consortium (VARC) [15] definitions as an absolute (<72 hr) reduction in kidney function and defined as: (1) an absolute increase in the highest value of SCr $\geq$ 0.3 mg dL^{-1} ($\geq$26.4 μmol L^{-1}) or (2) a percentage increase in the highest value of SCr $\geq$ 50% (1.5-fold from baseline). Patients who developed AKI were classified according to the degree of the severity of AKI in stage I (increase in SCr of 150–200% or increase of $\geq$0.3 mg dL^{-1} ($\geq$26.4 μmol L^{-1}), stage II (increase in SCr of 200–300%) or stage III (increase in SCr of $\geq$300 or increase of $\geq$4.0 mg dL^{-1} ($\geq$354 μmol L^{-1}) with an acute increase of $\geq$0.5 mg dL^{-1} (44 μmol L^{-1}).

Considering the possible association between procedural hypotensive periods with renal hypoperfusion and subsequent AKI, we documented procedural systolic and diastolic aortic pressures immediately after valve implantation as well as the occurrence of bleeding events due to any vascular complication. The latter was defined according to the VARC as (i) any aortic dissection; (ii) access site injury leading to death, $\geq$2 RBC transfusions, with or without percutaneous or surgical intervention, with or without irreversible end-organ damage; (iii) distal embolization (non-cerebral) from a vascular source leading or not leading to surgery, amputation or irreversible end-organ damage.

Anemia was defined according to the American College of Physicians and WHO criteria as a haemoglobin level <13 g dL^{-1} in men and <12 g dL^{-1} in women [16]. Thrombocytopenia was defined as a platelet count $<140 \times 10^9$/L. Data on RBC and platelet transfusions were recorded by the institutions' blood bank laboratory. All cause of death and cardiovascular death were collected.

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

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

death, excluding the patients who died during the procedure. In case a patient was transferred to the referring hospital, the LOS was defined as the total time spent in the treating and the referring center. Throughout this article, the terms "periprocedural" and "postprocedural" correspond to a time-frame of 24 and 72 hr after the start of the procedure, respectively.

Statistical Analysis

Categorical variables are presented as frequencies and percentages and were compared with the chi-square test or Fisher's exact test. The normality of distributions was assessed with the Shapiro-Wilk test; normal and skewed continuous variables are presented as means ± SD and medians (IQR), respectively. Comparison of continuous variables was done by using the Student's t tests or Wilcoxon's rank-sum test.

Kaplan–Meier methods were used to estimate survival rate and the Log-Rank test was performed to assess differences in survival among patients with and without AKI. A stepwise logistic regression analysis including all variables with $P < 0.05$ in the univariable analysis was used to determine the predictive factors of AKI and 30-day mortality. A stepwise Cox regression analysis including all variables with $P < 0.05$ in the Cox univariable analysis was used to determine the predictive factors of cumulative late mortality. For the purpose of the assessment of the prognostic value of periprocedural RBC transfusions and the occurrence of AKI, both variables were forced into the multivariable analyses for 30-day and late mortality, irrespective of the *P*-value obtained from the univariable analyses. A two-sided $P < 0.05$ was considered to indicate significance. All statistical analyses were performed with SPSS software (version 15).

RESULTS

A total of 126 patients underwent TAVI with the Medtronic CRS. Five patients who were on chronic haemodialysis before TAVI and three patients who died during the procedure were excluded from analysis leading to a final study population of 118 patients. The baseline characteristics and preprocedural clinical results dichotomized according to the presence or absence of AKI are presented in Table I. A similar table for periprocedural, postprocedural, and in-hospital results is shown in Table II.

AKI occurred in 22 patients (19%) of whom 2 patients (2%) underwent haemodialysis during hospital stay. The distribution of patients who developed AKI stage I, II, or III after TAVI according to the baseline GFR is shown in Fig. 1.

Predictive Factors of AKI

By univariable analysis, the patients with AKI had a higher frequency of previous myocardial infarction (55% vs. 19%, $P = 0.001$), coronary bypass surgery (46% vs. 21%, $P = 0.017$), low-flow low-gradient aortic stenosis (27% vs. 8%, $P = 0.023$) and thrombocytopenia (18% vs. 4%, $P = 0.039$), and showed a higher mean SCr (119 vs. 95 $\times$ 10^9 μmol L^{-1}, $P = 0.017$). They also received more periprocedural RBC transfusions (2.7 vs. 1.1 U, $P = 0.001$) and had a higher postprocedural leucocyte count (14.4 vs. 12.3 $\times$ 10^9/L, $P = 0.035$). Compared to those without AKI, patients with AKI received in total more RBC transfusions (4.4 vs. 1.8 U, $P < 0.001$) during their longer hospitalization period (17 vs. 9 days, $P < 0.001$). The independent predictors of AKI included: previous myocardial infarction (OR: 5.72; 95% CI: 1.64–19.94), periprocedural RBC transfusions (OR: 1.29; 95% CI: 1.01–1.70), postprocedural leucocyte count (OR: 1.18; 95% CI: 1.02–1.37) and logistic EuroSCORE (OR: 1.08; 95% CI: 1.01–1.14).

Predictive Factors of 30-Day Mortality

Overall, 30-day mortality was 8% (nine patients). It was significantly higher in patients with AKI compared to those patients without AKI (23% vs. 4%, respectively, $P = 0.011$). The causes of death in patients with AKI were sepsis (in two), heart failure necessitating intravenous diuretics (in two) and asystole at day 8 (one patient) due to an unrecognized alternating right and left bundle branch block after TAVI. The independent predictors of 30-day mortality were AKI (OR: 5.47; 95% CI: 1.23–24.21) and postprocedural leucocyte count (OR: 1.20; 95% CI: 1.03–1.38).

Predictive Factors of Cumulative Late Mortality

Clinical follow-up was available in all patients and ranged from 1 to 54 months, with a median (IQR) of 13 (5–24) months. A total of 33 patients (28%) died during the follow-up period, at a median (IQR) of 188 (30–385) days after TAVI. The cause of death was cardiovascular in 21 patients and non-cardiovascular in 12 patients. Among these, there was a borderline significant lower frequency of noncardiovascular death in patients without AKI in comparison to those with AKI (5/21 or 24% vs. 7/12 or 58%, $P = 0.054$). In the latter group, the causes for noncardiovascular death were sepsis (in two), terminal kidney failure, infection, hypovolemic shock, euthanasia and hypoglycaemia. For patients without AKI, noncardiovascular deaths were pneumonia (in two), diarrhea with dehydration

TABLE I. Baseline Characteristics According to the Presence or Absence of AKI Following TAVI

	Entire cohort ($n = 118$)	AKI ($n = 22$)	no AKI ($n = 96$)	P-value
Baseline patient characteristics				
Age (years), median (IQR)	82 (78–86)	83 (76–85)	82 (79–86)	0.61
Male, *n* (%)	53 (45)	11 (50)	42 (44)	0.60
Height (cm), mean ± SD	167 ± 8	169 ± 9	167 ± 8	0.38
Weight (kg), mean ± SD	73 ± 13	76 ± 13	72 ± 12	0.20
Body mass index, mean ± SD	26.0 ± 4.0	26.7 ± 3.8	25.9 ± 4.0	0.38
Body surface area (m^2), mean ± SD	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.18
NYHA class II, *n* (%)	17 (14)	2 (9)	15 (16)	0.74
NYHA class III, *n* (%)	83 (70)	14 (64)	69 (72)	0.45
NYHA class IV, *n* (%)	17 (14)	6 (27)	11 (12)	0.087
Previous cerebrovascular event, *n* (%)	29 (25)	6 (27)	23 (24)	0.75
Previous myocardial infarction, *n* (%)	30 (25)	12 (55)	18 (19)	0.001
Previous coronary artery bypass graft surgery, *n* (%)	30 (25)	10 (46)	20 (21)	0.017
Previous percutaneous coronary intervention, *n* (%)	32 (27)	6 (27)	26 (27)	0.99
Diabetes mellitus, *n* (%)	27 (23)	8 (36)	19 (20)	0.095
Hypertension, *n* (%)	53 (44)	11 (50)	42 (44)	0.60
Chronic obstructive pulmonary disease, *n* (%)	34 (29)	4 (18)	30 (31)	0.22
Permanent pacemaker, *n* (%)	13 (11)	2 (9)	11 (12)	1.0
Atrial fibrillation, *n* (%)	32 (27)	7 (32)	25 (26)	0.60
Logistic EuroSCORE (%), median (IQR)	12.3 (9.0–18.4)	18.4 (8.7–30.5)	12.1 (9.0–16.5)	0.052
STS score (%), median (IQR)	6.1 (3.7–12.6)	9.3 (3.9–13.8)	5.4 (3.6–12.5)	0.20
Multi-sliced computed tomography, *n* (%)	83 (70)	13 (59)	70 (73)	0.20
Baseline echocardiography				
Left ventricular ejection fraction (%), mean ± SD	51 ± 16	45 ± 15	52 ± 16	0.064
Aortic valve area (cm^2), mean ± SD	0.63 ± 0.2	0.67 ± 0.2	0.63 ± 0.2	0.31
Mean gradient, mean ± SD	47 ± 17	42 ± 17	48 ± 16	0.17
Low-flow low-gradient aortic stenosis, *n* (%)[a]	14 (12)	6 (27)	8 (8)	0.023
Mitral regurgitation grade ≥ III, *n* (%)	22 (19)	6 (27)	16 (17)	0.25
Aortic regurgitation grade ≥ III, *n* (%)	38 (32)	8 (36)	30 (31)	0.64
Baseline laboratory results				
Glomerular filtration rate (ml/min/1.73 m^2), mean ± SD	59 ± 18	54 ± 20	61 ± 18	0.11
Serum creatinine (μmol l^{-1}), mean ± SD	99 ± 43	119 ± 71	95 ± 32	0.017
Thrombocytopenia, *n* (%)	8 (7)	4 (18)	4 (4)	0.039
Leucocyte count (× 109/l), mean ± SD	7.4 ± 2.0	7.5 ± 2.0	7.4 ± 2.0	0.88
Anemia, *n* (%)	57 (48)	8 (36)	49 (51)	0.21
Baseline medication use				
Anti-platelets, *n* (%)	85 (76)	12 (67)	73 (79)	0.72
Diuretics, *n* (%)	71 (64)	14 (78)	57 (61)	0.40
ACE-inhibitors, *n* (%)	33 (30)	7 (39)	26 (28)	0.35
Angiotensin II antagonists, *n* (%)	25 (23)	3 (17)	22 (24)	0.80
Betablockers, *n* (%)	61 (55)	12 (67)	49 (53)	0.28
Calcium antagonists, *n* (%)	27 (24)	3 (17)	24 (26)	0.63

Abbreviations: ACE = angiotensin converting enzym; AKI = acute kidney injury; NYHA = New York Heart Association; RBC = red blood cell.
[a]Defined as a mean gradient <30 mm Hg in the presence of an aortic valve area <1cm^2.

(in two), and cancer. Univariable comparison of the patients who died during the follow-up in comparison to those who did not is shown in Table III. Multivariable analysis revealed that AKI was the only independent predictor of late mortality (HR: 2.79; 95% CI: 1.36–5.71). Kaplan–Meier survival curves for patients with and without AKI are presented in Fig. 2.

DISCUSSION

We found that AKI occurred in 19% of the patients following TAVI of whom 2% needed temporary haemodialysis. Predictive factors of AKI included previous myocardial infarction, periprocedural RBC transfusion, postprocedural leucocyte count and logistic EuroSCORE. AKI was associated with a longer hospital stay and was found to be an independent predictor of both 30-day and cumulative late mortality.

The occurrence of AKI following TAVI in this study is consistent with the observations of Aregger et al. [10] and Bagur et al. [11] who found a frequency of 28 and 12% in a series of 58 and 213 patients, respectively. Of note, the definitions of AKI in these studies (RIFLE criteria) were almost similar to the herein reported VARC criteria except for the time at which AKI was defined; 72 hr in this study compared to 48 hr

TABLE II. Periprocedural, Postprocedural, and In-Hospital Outcomes According to the Presence or Absence of AKI Following TAVI

	Entire cohort (n = 118)	AKI (n = 22)	no AKI (n = 96)	P-value
Periprocedural (<24 hr after start procedure)				
Aortic systolic pressure (mm Hg), mean ± SD	139 ± 34	133 ± 27	140 ± 36	0.47
Aortic diastolic pressure (mm Hg), mean ± SD	54 ± 13	53 ± 19	52 ± 12	0.90
Any vascular complication, n (%)	22 (19)	7 (32)	15 (16)	0.079
Contrast volume (ml), mean ± SD	199 ± 81	213 ± 56	196 ± 86	0.42
RBC transfusions, mean ± SD	1.4 ± 2.0	2.7 ± 3.6	1.1 ± 1.3	0.001
Platelet transfusions ≥ 1, n (%)	6 (5)	2 (9)	4 (4)	0.34
Duration of procedure (min), mean ± SD	247 ± 79	271 ± 82	241 ± 78	0.12
Postprocedural (<72 hrs after start procedure)				
Glomerular filtration rate (ml/min/1.73 m^2), mean ± SD				
Preprocedural	59 ± 18	54 ± 19	61 ± 18	0.11
Postprocedural	57 ± 21	34 ± 16	62 ± 19	<0.001
Serum creatinine (μmol l^{-1}), mean ± SD				
Preprocedural	99 ± 43	119 ± 71	95 ± 32	0.017
Postprocedural	111 ± 59	182 ± 87	95 ± 33	<0.001
Leucocyte count (× 109/l), mean ± SD				
Preprocedural	7.4 ± 2.0	7.5 ± 2.0	7.4 ± 2.0	0.88
Postprocedural	12.7 ± 4.1	14.4 ± 4.2	12.3 ± 4.0	0.035
Anemia, n (%)				
Preprocedural	57 (48)	8 (36)	49 (51)	0.21
Postprocedural	115 (98)	22 (100)	93 (97)	1.0
Thrombocytopenia, n (%)				
Preprocedural	8 (7)	4 (18)	4 (4)	0.039
Postprocedural	56 (48)	14 (64)	42 (44)	0.092
In-hospital				
RBC transfusions, mean ± SD	2.3 ± 2.7	4.4 ± 4.3	1.8 ± 1.8	<0.001
LOS (days), median (IQR)	10 (8–18)	17 (11–30)	9 (7–14)	<0.001
Mortality				
30-day, n (%)	9 (8)	5 (23)	4 (4)	0.011
Cumulative late, n (%)	33 (28)	12 (55)	21 (22)	0.002

Abbreviations: AKI = acute kidney injury; LOS = length of stay; RBC = red blood cell.

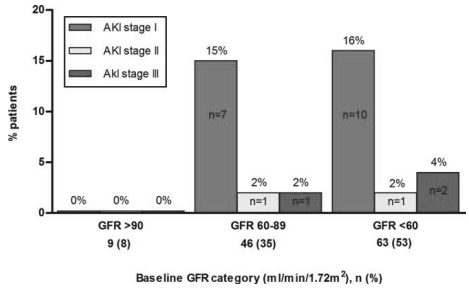


Fig. 1. Distribution of patients who developed AKI stage I, II, or III according to the baseline GFR category. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in the other studies. The variation in the point estimates is also explained by the differences in the number of patients in whom AKI was determined and type of patient. Aregger et al. [10] for instance also included two patients who were on chronic haemodialysis.

We found a number of patient- (antecedent myocardial infarction, EuroSCORE) and procedure-related (RBC transfusion) predictors of AKI in addition to leucocyte count after TAVI. The EuroSCORE, which is a conglomerate of a number of patient-related variables, was entered into the model. This may have precluded the identification of individual patient-related variables such as pre-existing renal impairment. Indeed, preprocedural SCr was found to be an independent predictor of AKI when the EuroSCORE was left out of the model (OR: 1.01; 95% CI: 1.00–1.03).

A previous myocardial infarction was found to be the most powerful predictor of AKI. In addition, those with a history of myocardial infarction as well as the patients that developed AKI more frequently showed worse left ventricular ejection fractions (45% vs. 52%, P = 0.064 and 45% vs. 53%, P = 0.032, respectively) and were more likely to have low-flow, low-gradient aortic stenosis (17% vs. 10%, P = 0.34 and 27% vs. 8%, P = 0.023) compared to patients without myocardial infarction and AKI. From a pathophysiologic point of view, this may reflect that these patients have an impaired cardio-circulatory homeostasis and, therefore,

TABLE III. Baseline Characteristics and Periprocedural, Postprocedural, and In-Hospital Results According to the Occurrence of Cumulative Late Mortality Following TAVI

	Cumulative late mortality ($n = 33$)	Cumulative late survival ($n = 85$)	*P*-value
Baseline patient characteristics			
Age (years), median (IQR)	82 (76–86)	83 (79–86)	0.50
Male, *n* (%)	20 (61)	33 (39)	0.033
Height (cm), mean ± SD	169 ± 8	167 ± 8	0.23
Weight (kg), mean ± SD	74 ± 12	73 ± 13	0.79
Body mass index, mean ± SD	25.8 ± 3.7	26.1 ± 4.1	0.69
Body surface area (m^2), mean ± SD	1.85 ± 0.2	1.82 ± 0.2	0.56
NYHA class II, *n* (%)	3 (9)	14 (17)	0.39
NYHA class III, *n* (%)	21 (64)	62 (73)	0.32
NYHA class IV, *n* (%)	9 (27)	8 (9)	0.020
Previous cerebrovascular event, *n* (%)	9 (27)	20 (24)	0.67
Previous myocardial infarction, *n* (%)	11 (33)	19 (22)	0.22
Previous coronary artery bypass graft surgery, *n* (%)	10 (30)	20 (24)	0.45
Previous percutaneous coronary intervention, *n* (%)	6 (18)	26 (31)	0.17
Diabetes mellitus, *n* (%)	9 (27)	18 (21)	0.48
Hypertension, *n* (%)	16 (49)	37 (44)	0.63
Chronic obstructive pulmonary disease, *n* (%)	11 (33)	23 (27)	0.50
Permanent pacemaker, *n* (%)	5 (15)	8 (10)	0.51
Atrial fibrillation, *n* (%)	9 (28)	23 (27)	0.91
Logistic EuroSCORE (%), median (IQR)	14.3 (9.5–21.7)	12.1 (8.9–16.6)	0.19
STS score (%), median (IQR)	5.1 (3.3–7.5)	7.0 (3.9–14.4)	0.044
Baseline echocardiography			
Left ventricular ejection fraction (%), mean ± SD	46 ± 15	53 ± 16	0.042
Aortic valve area (cm^2), mean ± SD	0.66 ± 0.21	0.62 ± 0.18	0.36
Mean gradient, mean ± SD	50 ± 15	45 ± 17	0.22
Low-flow low-gradient aortic stenosis, *n* (%)[a]	3 (9)	11 (13)	0.78
Mitral regurgitation grade ≥ III, *n* (%)	8 (24)	14 (17)	0.33
Aortic regurgitation grade ≥ III, *n* (%)	13 (39)	25 (29)	0.30
Periprocedural (<24 hrs after start procedure)			
Any vascular complication, *n* (%)	5 (15)	17 (20)	0.49
Contrast volume (ml), mean ± SD	205 ± 73	196 ± 85	0.60
RBC transfusions, mean ± SD	2.0 ± 2.8	1.2 ± 1.6	0.074
Platelet transfusions ≥ 1, *n* (%)	1 (3)	5 (6)	1.0
Duration of procedure (min), mean ± SD	254 ± 76	243 ± 81	0.54
Postprocedural (<72 hrs after start procedure)			
Glomerular filtration rate (ml/min/1.73 m^2), mean ± SD			
Preprocedural	58 ± 18	60 ± 18	0.75
Postprocedural	50 ± 22	60 ± 20	0.022
Serum creatinine (μmol l^{-1}), mean ± SD			
Preprocedural	106 ± 41	97 ± 43	0.31
Postprocedural	134 ± 64	103 ± 55	0.009
Leucocyte count (×109/l), mean ± SD			
Preprocedural	7.7 ± 2.0	7.3 ± 1.9	0.35
Postprocedural	13.8 ± 5.1	12.2 ± 3.6	0.064
Anemia, *n* (%)			
Preprocedural	20 (61)	37 (44)	0.096
Postprocedural	33 (100)	82 (97)	0.56
Thrombocytopenia, *n* (%)			
Preprocedural	4 (12)	4 (5)	0.22
Postprocedural	15 (46)	41 (48)	0.79
In-hospital			
RBC transfusions, mean ± SD	3.1 ± 3.6	2.0 ± 2.2	0.042
Acute kidney injury, *n* (%)	12 (36)	10 (12)	0.002
LOS (days), median (IQR)	14 (8–25)	10 (8–14)	0.19

Abbreviations: AKI = acute kidney injury; LOS = length of stay; NYHA = New York Heart Association; RBC = red blood cell.
[a]Defined as a mean gradient <30 mm Hg in the presence of an aortic valve area <1cm^2.

more difficulties in maintaining adequate renal perfusion during TAVI which is known to be associated with episodes of haemodynamic alterations. Although we could not confirm the latter with blood pressure data that were obtained after complete prosthesis release, it is likely that other phases of the procedure

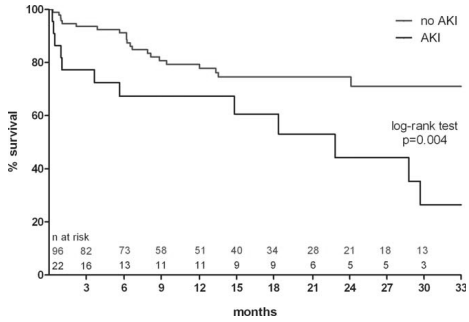


Fig. 2. Kaplan–Meier survival rates stratified for the presence and absence of AKI in patients undergoing TAVI (The Log-Rank was used for comparison of survival rates). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

such as rapid right ventricular pacing during predilatation of the native aortic valve may have induced such kidney affecting hypotensive periods. For these reasons, close monitoring of procedural blood pressures with adequate treatment in the case of sudden pressure decline may be necessary in these patients.

In accordance with Aregger et al. [10] and Bagur et al. [11], we found that RBC transfusion independently predicted AKI following TAVI. Whether there is a relationship between the number of RBC transfusions and the severity of AKI, as observed in the univariable analysis remains to be elucidated. This study may have lacked the power to exclude confounders. Of note, a relation between the number of RBC transfusions and multi organ failure has been reported in trauma patients [19]. Since RBC transfusion is associated with the coadministration of a number of other molecular and cellular substances [17] such as interleukin-8 which typically accumulates in stored packed red cells causing transient leucocytosis [18], the observed association between increased leucocyte count and AKI is most likely a direct result of the transfusion rather than being a cause of AKI.

Although the mean volume of contrast media used in the present study was twice as high compared to the results from Bagur et al. [11] (199 vs. 97 mL), we were unable to find an association with the occurrence of AKI. This is even more noteworthy since we measured AKI at 72 hr as outlined by the VARC instead of 48 hr. It is known that the increase in SCr reaches its peak at about 3–5 days after contrast exposure [20]. Despite the longer window of analysis in this study, we still failed to observe a relationship. A reason for this may be associated with the fact that patients suffering from pre-existing renal failure (who were found to be at risk for AKI as identified from the multivariable analysis when EuroSCORE was excluded) tended to receive less amounts of contrast volumes compared to patients without pre-existing renal failure (187 vs. 212 mL, $P = 0.14$). Importantly, the deleterious implications of contrast-induced nephropathy after percutaneous coronary intervention (PCI) are well known and, therefore, minimization of the use of these agents is warranted [21–23].

Similar to many reports on patients who underwent cardiac surgery and PCI, we found AKI to be an independent predictor of both 30-day and cumulative late mortality [2,4,7,22–28]. Bagur et al. [11] is the only study that determined the impact of AKI following TAVI on mortality and found AKI to be an independent predictor of 30-day mortality. The present study shows that relative to patients without AKI, non-cardiovascular causes of death were more common in those with AKI and included sepsis (in 2) at Day 11 and 29; terminal kidney failure at Day 450; and infection, hypovolemic shock, euthanasia and hypoglycaemia at Days 172, 567, 694, and 873, respectively. The first three deaths were possibly related with postprocedural AKI whereas non-cardiovascular deaths in patients without AKI were less likely to be associated with renal dysfunction (pneumonia in two, diarrhea with dehydration in two, and cancer in one). These findings may reflect important consequences of AKI following TAVI that require close monitoring in the early postprocedural days and even after hospital discharge.

Considering the prognostic effects of AKI and the role of RBC transfusion in the development of AKI as observed in both this study and, perhaps more importantly the one of Bagur et al. [11] given the observed odds ratio and 95% CI (this study: 1.4 [1.0–1.8], Bagur et al.: 3.5 [1.3–9.3]), it emphasizes the importance of a strict surgical discipline in the execution of TAVI by—among others—strict control of haemostasis. Vascular access site complications, which are the most common cause of bleeding, are reported to occur in up to 34% of the patients [29–32]. Despite our meticulous effort to ensure proper entry of the common femoral artery by echo-guided puncture and closure with the Prostar system, 19% of our patients suffered from a vascular complication. These patients in particular are at increased risk for both renal hypoperfusion and RBC transfusion. Both these factors were associated with AKI by univariable analysis, but only transfusion was found to be an independent predictor of AKI. Although this may suggest a causative mechanism of transfusion rather than of hypotension-related vascular complications, we sought to evaluate the potential confounding effects of vascular complication by including this

factor in the multivariable analysis for AKI predictors. This, however, did not change the model. The high frequency of vascular complications nevertheless expresses the need of improvement of this part of the procedure. It is the reason why some advocate a limited surgical cut-down of the femoral artery that consists of the exposure of the ventral side of the femoral artery without a complete dissection of the artery free of its surrounding supportive structures.

Improvement can also be obtained by changes in the patient selection, pre- and perioperative management. Bagur et al. [11] found chronic obstructive disease and hypertension to be independently associated with AKI while we found previous myocardial infarction. Patients with a history of myocardial infarction and/or impaired ejection fractions may benefit from close blood pressure monitoring during the procedure with adequate treatment in the case of sudden instability of pressures. Regarding RBC transfusions, we changed our practice to a more restrictive strategy which seems beneficial but challenging given the high prevalence of anemia at presentation (48%) in these patients. Despite this, we found that the first half of our patient cohort received on average 2.1 RBC transfusions whereas later treated patients received on average 1.3 units, while our vascular complication rates only showed a small reduction from 20% to 16%. Also, more awareness among the potential impact of contrast on the occurrence of AKI in these multimorbid patients who often present with pre-existing renal failure is warranted and should be addressed with a dedicated prehydration protocol. Finally, patients diagnosed with AKI after TAVI require close monitoring during the early postprocedural days and thereafter since they are at increased risk of worse survival.

Limitations

The data used for this study were prospectively collected and analyses were performed on a relatively small sample size with a small number of outcome events. As a result, potential model overfitting and overparamterization may have affected the results which therefore constitutes an important limitation of this study. However, this may have had a minor impact since the direction of outcome is consistent with previous reports of Aregger et al. and Bagur et al.

CONCLUSION

AKI following TAVI occurred in 19% of the patients. In addition to patient-related variables and leucocyte count after TAVI, RBC transfusion was found to be an independent predictor of AKI, which in turn predicted both 30-day and cumulative late mortality. It remains to be elucidated whether improvement in patient selection, pre- and perioperative management reduce AKI.

REFERENCES

1. Edwards F, Peterson E, Coombs L, DeLong E, Jamieson W, Shroyer ALW, Grover F. Prediction of operative mortality after valve replacement surgery. J Am Coll Cardiol 2001;37:885–892.
2. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann L, Druml W, Bauer P, Hiesmayr M. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. J Am Soc Nephrol 2004;15:1597–1605.
3. Wijeysundera D, Rao V, Beattie W, Ivanov J, Karkouti K. Evaluating surrogate measures of renal dysfunction after cardiac surgery. Anesth Analg 2003;96:1265–1273.
4. Chertow G, Levy E, Hammermeister K, Grover F, Daley J. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998;104:343–348.
5. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: Evaluation of the RIFLE classification. Ann Thorac Surg 2006;81:542–546.
6. Loef B, Epema A, Smilde T, Henning R, Ebels T, Navis G, Stegeman C. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. J Am Soc Nephrol 2005;16:195–200.
7. Ryckwaert F, Boccara G, Frappier J, Colson P. Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. Crit Care Med 2002;30:1495–1498.
8. Karkouti K, Wijeysundera D, Yau T, Callum J, Cheng D, Crowther M, Dupuis J, Fremes S, Kent B, Laflamme C, et al. Acute kidney injury after cardiac surgery: Focus on modifiable risk factors. Circulation 2009;119:495–502.
9. Koch C, Li L, Duncan A, Mihaljevic T, Cosgrove D, Loop F, Starr N, Blackstone E. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. Crit Care Med 2006;34:1608–1616.
10. Aregger F, Wenaweser P, Hellige G, Kadner A, Carrel T, Windecker S, Frey F. Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. Nephrol Dial Transplant 2009;24:2175–2179.
11. Bagur R, Webb J, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson J, Gutiérrez M, Clavel M, Bertrand O, et al. Acute kidney injury following transcatheter aortic valve implantation: Predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2010;31:865–874.
12. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, Sauren B, Mohr F, Walther T, Zickmann B, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: Device success and 30-day clinical outcome. J Am Coll Cardiol 2007;50:69–76.
13. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: Results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242–249.

14. Levey A, Eckardt K, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter T, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005;67:2089–2100.
15. Serruys PW, Piazza N, van Mieghem N, Leon MB. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: Valve Academic Research Consortium consensus on event definition. Presented EuroPCR May 27, 2010, Paris.
16. McKechnie R, Smith D, Montoye C, Kline-Rogers E, O'Donnell M, DeFranco A, Meengs W, McNamara R, McGinnity J, Patel K, et al. Prognostic implication of anemia on in-hospital outcomes after percutaneous coronary intervention. Circulation 2004;110:271–277.
17. Spiess B. Transfusion of blood products affects outcome in cardiac surgery. Semin Cardiothorac Vasc Anesth 2004;8:267–281.
18. Izbicki G, Rudensky B, Na'amad M, Hershko C, Huerta M, Hersch M. Transfusion-related leukocytosis in critically ill patients. Crit Care Med 2004;32:439–442.
19. Moore F, Moore E, Sauaia A, Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 1997;132:620–624; discussion 624–625.
20. Asif A, Epstein M. Prevention of radiocontrast-induced nephropathy. Am J Kidney Dis 2004;44:12–24.
21. Del Duca D, Iqbal S, Rahme E, Goldberg P, de Varennes B. Renal failure after cardiac surgery: Timing of cardiac catheterization and other perioperative risk factors. Ann Thorac Surg 2007;84:1264–1271.
22. Rihal C, Textor S, Grill D, Berger P, Ting H, Best P, Singh M, Bell M, Barsness G, Mathew V, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002;105:2259–2264.
23. Thomsen H, Morcos S, Barrett B. Contrast-induced nephropathy: The wheel has turned 360 degrees. Acta Radiol 2008;49:646–657.
24. Conlon P, Stafford-Smith M, White W, Newman M, King S, Winn M, Landolfo K. Acute renal failure following cardiac surgery. Nephrol Dial Transplant 1999;14:1158–1162.
25. Hobson C, Yavas S, Segal M, Schold J, Tribble C, Layon A, Bihorac A. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009;119:2444–2453.
26. Mangano C, Diamondstone L, Ramsay J, Aggarwal A, Herskowitz A, Mangano D. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998;128:194–203.
27. McCullough P, Wolyn R, Rocher L, Levin R, O'Neill W. Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. Am J Med 1997;103:368–375.
28. Mehta R, Grab J, O'Brien S, Bridges C, Gammie J, Haan C, Ferguson T, Peterson E, Investigators SoTSNCSD. Bedside tool for predicting the risk of postoperative dialysis in patients undergoing cardiac surgery. Circulation 2006;114:2208–2216; quiz 2208.
29. Ducrocq G, Francis F, Serfaty J, Himbert D, Maury J, Pasi N, Marouene S, Provenchère S, Iung B, Castier Y, et al. Vascular complications of transfemoral aortic valve implantation with the Edwards SAPIEN prosthesis: Incidence and impact on outcome. EuroIntervention 2010;5:666–672.
30. Kahlert P, Al-Rashid F, Weber M, Wendt D, Heine T, Kottenberg E, Thielmann M, Kühl H, Peters J, Jakob H, et al. Vascular access site complications after percutaneous transfemoral aortic valve implantation. Herz 2009;34:398–408.
31. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, Soula P, Gabiache Y, Fournial G, Marcheix B, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. EuroIntervention 2010;5:659–665.
32. Van Mieghem N, Nuis R, Piazza N, Apostolos T, Ligthart J, Schultz C, de Jaegere P, Serruys P. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: The Rotterdam experience. EuroIntervention 2010;5:673–679.

CHAPTER 11

Blood tranfusion and the risk of acute kidney injury following transcatheter aortic valve implantation

Blood Transfusion and the Risk of Acute Kidney Injury After Transcatheter Aortic Valve Implantation

Rutger-Jan Nuis, MSc; Josep Rodés-Cabau, MD; Jan-Malte Sinning, MD; Leen van Garsse, MD; Joelle Kefer, MD, PhD; Johan Bosmans, MD, PhD; Antonio E. Dager, MD; Nicolas van Mieghem, MD; Marina Urena, MD; Georg Nickenig, MD, PhD; Nikos Werner, MD, PhD; Jos Maessen, MD, PhD; Parla Astarci, MD; Sergio Perez, MD; Luis M. Benitez, MD; Eric Dumont, MD; Ron T. van Domburg, PhD; Peter P. de Jaegere, MD, PhD

Background—Blood transfusion is associated with acute kidney injury (AKI) after transcatheter aortic valve implantation (TAVI). We sought to elucidate in more detail the relation between blood transfusion and AKI and its effects on short- and long-term mortality.

Methods and Results—Nine hundred ninety-five patients with aortic stenosis underwent TAVI with the Medtronic CoreValve or the Edwards Valve in 7 centers. AKI was defined by the Valve Academic Research Consortium (absolute increase in serum creatinine ≥0.3 mg/dL [≥26.4 μmol/L] or ≥50% increase ≤72 hours). Logistic and Cox regression was used for predictor and survival analysis. AKI occurred in 20.7% (n=206). The number of units of blood transfusion ≤24 hours was the strongest predictor of AKI (≥5 units, OR, 4.81 [1.45–15.95], 3–4 units, OR, 3.05 [1.24–7.53], 1–2 units, OR, 1.47 [0.98–2.22]) followed by peripheral vascular disease (OR, 1.48 [1.05–2.10]), history of heart failure (OR, 1.43 [1.01–2.03]), leucocyte count ≤72 hours after TAVI (OR, 1.05 [1.02–1.09]) and European System for Cardiac Operative Risk Evaluation (EuroSCORE; OR, 1.02 [1.00–1.03]). Potential triggers of blood transfusion such as baseline anemia, bleeding-vascular complications, and perioperative blood loss were not identified as predictors. AKI and life-threatening bleeding were independent predictors of 30-day mortality (OR, 3.15 [1.56–6.38], OR, 6.65 [2.28–19.44], respectively), whereas transfusion (≥3 units), baseline anemia, and AKI predicted mortality beyond 30 days.

Conclusions—AKI occurred in 21% of the patients after TAVI. The number of blood transfusions but not the indication of transfusion predicted AKI. AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality. These findings indicate that outcome of TAVI may be improved by more restrictive use of blood transfusions. **(*Circ Cardiovasc Interv*. 2012;5:680-688.)**

Key Words: acute kidney injury ■ anemia ■ blood transfusion ■ predictors ■ transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis, who are considered at high risk for surgical aortic valve replacement.[1] Despite its minimally invasive nature, TAVI is invariably associated with a number of complications that may affect outcome. Some of these complications are clinically manifest during the procedure for which immediate actions are taken, whereas others such as acute kidney injury (AKI) are detected later and may have silent, but harmful, prognostic effects. AKI is reported in 12% to 57% of the patients who undergo TAVI and is associated with a 2- to 6-fold increased risk of death during short- and long-term follow-up.[2–10]

At present, the pathophysiologic mechanisms of AKI after TAVI are unclear. Some studies suggest a direct relation between perioperative blood transfusion and AKI.[5,6,10] This may be explained by the fact that in association with the transfusion of red blood cells (RBC) a number of other cellular and molecular substances are administrated that either directly or indirectly (eg, inflammation) induce kidney damage,[11] yet one may question whether the triggers for blood transfusion, such as perioperative blood loss because of bleeding-vascular

Received March 21, 2012; accepted August 17, 2012.

From the Department of Cardiology, ThoraxCenter, Erasmus Medical Center, Rotterdam, Netherlands (R-J.N., N.v.M., R.T.v.D., P.P.d.J.); Department of Cardiology, Quebec Heart and Lung Institute, Quebec City, Canada (J.R-C., M.U., E.D.); Department of Medicine II—Cardiology, University Hospital Bonn, Bonn, Germany (J-M.S, G.N., N.W.); Department of Cardiothoracic Surgery, University Hospital Maastricht, The Netherlands (L.v.G., J.M.); Department of Cardiology, University Hospital Saint-Luc, Brussels, Belgium (J.K., P.A.); Department of Cardiology, University Hospital Antwerp, Antwerp, Belgium (J.B.); and Department of Cardiology, Angiografia de Occidente S.A., Cali, Colombia (A.E.D., S.P., L.M.B.).

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.112.971291/-/DC1.

Correspondence to Peter P de Jaegere, MD, PhD, Thoraxcenter, Erasmus University Medical Center, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands. E-mail p.dejaegere@erasmusmc.nl

WHAT IS KNOWN

- Perioperative blood transfusion has been associated with acute kidney injury after transcatheter aortic valve implantation.

WHAT THE STUDY ADDS

- Blood transfusion was the most important factor associated with acute kidney injury whereas potential triggers of transfusion, such as baseline anemia, vascular-bleeding complications, blood loss, or severe hypotension, were not.
- Patients with anemia had less decline in hemoglobin after transcatheter aortic valve implantation but received more transfusions as compared with patients without anemia.
- Acute kidney injury was a predictor of both short- and long-term mortality whereas blood transfusion predicted long-term mortality.

complications may also play a role. This also holds for the presence of baseline anemia, impaired kidney function, and other procedural factors such as changes in cardiovascular hemodynamics during TAVI.[7,12] We, therefore, sought to explore in more detail the relation between blood transfusion and AKI after TAVI relative to a number of baseline and procedural variables in a series of 995 patients in addition to the effects of blood transfusion and AKI on mortality.

Methods

Patients

Between November 2005 and January 2012, 1050 patients with aortic stenosis underwent TAVI with the Medtronic CoreValve System (Medtronic Inc) or the Edwards SAPIEN Valve (Edwards Life Sciences) in the Erasmus Thoraxcenter, Rotterdam, The Netherlands (n=220); Quebec Heart and Lung Institute, Quebec City, Quebec, Canada (n=216); University Hospital Bonn, Bonn, Germany (n=182); University Hospital Maastricht, Maastricht, The Netherlands (n=145); University Hospital Saint-Luc, Brussels, Belgium (n=122); University Hospital Antwerp, Antwerp, Belgium (n=97); and Angiografia de Occidente, Cali, Colombia (n=68). Patients on chronic hemodialysis (n=35) and those who died within 72 hours precluding creatinine measurements during the first 3 days after TAVI (n=23—including 3 patients on chronic hemodialysis [causes of death are listed in online-only Data Supplement]) were excluded from the study. The final study population consisted, therefore, of 995 patients.

In each institution, patients with symptomatic aortic stenosis were screened at the outpatient clinic during which a structured interview, physical examination, ECG, and blood sampling were performed. Invasive diagnostic workup included a left heart catheterization (performed by the referring institution in most patients) to determine the coronary anatomy and hemodynamic status; echo-(Doppler) cardiography (transthoracic or transesophageal), contrast angiography, or contrast enhanced multisliced CT were performed >2 weeks before TAVI to assess the valvular and vascular anatomy and to define the vascular access strategy (transfemoral, transapical, transsubclavian, transaortic). Treatment eligibility was based on previously described patient-selection criteria, and final acceptance for TAVI was established by Heart Team consensus.[13]

In accordance with the institutions policies, every patient gave written informed consent for TAVI and the use of anonymous clinical, procedural and follow-up data for research in accordance with Institutional Review Board approval. This study complies with the Declaration of Helsinki.

Procedure

TAVI was performed under general or local anesthesia using the Medtronic CoreValve System (26, 29, or 31 mm) or Edwards SAPIEN Valve (20, 23, or 26 mm) via a transfemoral, transapical, transsubclavian, or transaortic approach of which details have been described previously.[14–18] Details of the prehydration protocol for the various institutions are summarized in online-only Data Supplement.

The amount of contrast and the occurrence of life-threatening arrhythmias (any episode of ventricular tachycardia, ventricular fibrillation, asystole requiring vasopressive drugs, electric defibrillation, or cardiopulmonary resuscitation), any complication leading to severe sustained hypotension, postimplantation balloon dilation, and (Valve Academic Research Consortium-defined) bleeding and vascular complications were recorded during or immediately after TAVI.[19]

After the procedure, patients were extubated in the catheterization room or after transfer in the cardiac care unit shortly after the procedure or later if clinically indicated. Antiplatelet therapy after Medtronic CoreValve System and Edwards SAPIEN Valve implantation consisted of clopidogrel 75 mg for 6 months and aspirin 80 to 100 mg indefinitely. Patients on oral anticoagulant therapy before TAVI received periprocedural therapeutic anticoagulation with unfractionated heparin or low-molecular-weight heparin in combination with either clopidogrel or aspirin to cover the time with subtherapeutic INR levels. Oral anticoagulation was resumed shortly after TAVI.

Laboratory Measurements and AKI Definition

Preoperative serum creatinine (SCr) values were used to calculate the baseline SCr clearance using the Cockcroft and Gault equation: SCr clearance (mL/min)=(140−age)×weight (kg)÷72×SCr (mg/dL) (×0.85 for women).[20] Chronic kidney disease (CKD) was defined as a calculated SCr clearance <60 mL/min.[21,22] Patients with CKD were further classified in tertiles to examine the effect of mild (45.0–60.0 mL/min), moderate (35.0–44.9 mL/min), and severe CKD (<35 mL/min).

AKI was defined according to the Valve Academic Research Consortium recommendations as an absolute (≤72 hours) reduction in kidney function and defined as: (1) an absolute increase in the highest value of SCr ≥0.3 mg/dL (≥26.4 μmol/L) or (2) a percentage increase in the highest value of SCr ≥50% (1.5-fold from baseline). AKI severity was further classified as stage I (increase in SCr of 150%–200% or increase of ≥0.3 mg/dL ≥26.4 μmol/L]), stage II (increase in SCr of 200%–300%), or stage III (increase in SCr of ≥300% or increase of ≥4.0 mg/dL [≥354 μmol/L]) with an acute increase of ≥0.5 mg/dL (44 μmol/L). Patients receiving renal replacement therapy (hemodyalysis, peritoneal dialysis, or hemofiltration) during hospitalization or within 30 days after the procedure were considered to be classified as stage III.[19]

Preoperative hemoglobin (Hb) values were used to define baseline anemia according to the American College of Physicians and WHO criteria as a Hb level <13 g/dL in men and <12 g/dL in women.[23] Patients with anemia were classified in tertiles to assess the effects of mild (12.0–12.99 g/dL in men; 11.30–11.99 g/dL in women), moderate (10.80–11.99 g/dL in men; 10.23–11.29 g/dL in women), and severe anemia (<10.80 g/dL in men, <10.23 g/dL in women).

Data on RBC transfusions were recorded by the institution's blood bank laboratory and used to determine the corrected Hb drop ≤24 hours after TAVI according to the modified Landefeld equation.[24,25] In this equation 1 unit of packed RBCs is considered to represent 1 g/dL of Hb and, therefore, the net Hb drop corresponds to the addition of the number of packed RBC to the baseline-minus-measured nadir Hb.[12]

Follow-Up

After hospital discharge, mortality data were collected by contacting the civil registries or the referring physician or general practitioner

Table 1. Baseline Characteristics of Patients With and Without AKI After TAVI

	Entire Cohort (n=995)	No AKI (n=789)	AKI (n=206)	*P* Value
Age, y, median (IQR)	82 (77–86)	82 (78–86)	82 (77–86)	0.42
Male sex, no (%)	497 (50)	393 (50)	104 (50)	0.86
Height, cm, mean±SD	164±10	164±10	165±10	0.31
Weight, kg, mean±SD	72±15	71±15	73±16	0.092
Body mass index, mean±SD	26.4±5.0	26.3±4.8	26.9±5.5	0.14
Body surface area, mean±SD	1.79±0.21	1.79±0.21	1.82±0.22	0.097
New York Heart Association class ≥III, no (%)	806 (81)	631 (80)	175 (85)	0.11
Previous cerebrovascular event, no (%)	198 (20)	155 (20)	43 (21)	0.71
Previous myocardial infarction, no (%)	262 (26)	201 (26)	61 (30)	0.23
Previous coronary artery bypass graft surgery, no (%)	267 (27)	214 (27)	53 (26)	0.68
Previous percutaneous coronary intervention, no (%)	303 (31)	239 (30)	64 (31)	0.83
Congestive heart failure, no (%)	577 (58)	442 (56)	135 (66)	0.010
Diabetes mellitus, no (%)	274 (28)	218 (28)	56 (27)	0.90
Hypertension, no (%)	772 (78)	603 (76)	169 (82)	0.085
Peripheral vascular disease, no (%)	301 (30)	222 (28)	79 (39)	0.004
Chronic obstructive pulmonary disease, no (%)	281 (28)	217 (28)	64 (31)	0.31
Creatinine, median (IQR)	100 (81–129)	99 (81–126)	106 (80–139)	0.12
Chronic kidney disease, no (%)*				
Mild*	243 (24)	198 (25)	45 (22)	0.40
Moderate*	250 (25)	203 (26)	47 (23)	
Severe*	242 (24)	184 (23)	58 (28)	
Hemoglobin, mean±SD	12.2±3.8	12.2±4.2	12.0±1.7	0.42
Anemia, no (%)†				
Mild†	200 (20)	157 (20)	43 (21)	0.82
Moderate†	192 (19)	150 (19)	42 (20)	
Severe†	175 (18)	136 (17)	39 (19)	
Leucocyte count ($\times 10^9$ cells/L), mean±SD	7.3±2.0	7.3±2.2	7.2±2.1	0.55
Atrial fibrillation, no (%)	265 (27)	209 (27)	56 (27)	0.82
Permanent pacemaker, no (%)	133 (13)	100 (13)	33 (16)	0.21
Left ventricular ejection fraction ≤35%, no (%)	157 (16)	116 (15)	41 (20)	0.068
Aortic valve area, cm^2, mean±SD	0.66±0.19	0.66±0.20	0.66±0.17	0.89
Peak gradient, mean±SD	71±25	71±25	71±26	0.93
Mitral regurgitation grade ≥III, no (%)	118 (12)	102 (13)	16 (8)	0.041
Aortic regurgitation grade ≥III, no (%)	86 (9)	71 (9)	15 (7)	0.44
Logistic Euroscore, median (IQR)	17 (11–30)	15 (10–28)	22 (12–35)	<0.001

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; and IQR, interquartile range.

*Chronic kidney disease was defined as a calculated creatinine clearance <60 mL/min; mild 45.0 to 60.0 mL/min, moderate 35.0 to 44.9 mL/min and severe <35 mL/min.

†Anemia was defined as Hb <13 g/dL in men and <12 g/dL in women,[23] mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia <10.80 g/dL in men and <10.23 g/dL in women.

and was complete in 98.4% of the 937 patients who survived the first 30 days (median [interquartile range] follow-up time; 12 [4–23] months). Death at any time during the follow-up period was classified as cardiac or noncardiac according to the Valve Academic Research Consortium criteria.[19]

Statistical Analysis

Details of data completeness and management are summarized in online-only Data Supplement. Categorical variables are presented as frequencies and percentages and were compared with the χ^2 test or Fisher exact test. The normality of distributions was assessed with the Shapiro-Wilk test; comparison of continuous variables was done by using the Student *t* test or Wilcoxon rank-sum test when appropriate. A stepwise logistic regression analysis including all variables from Tables 1 and 2 exhibiting $P<0.10$ in the univariable analysis was used to determine the predictive factors of AKI and 30-day mortality. Two interaction terms were tested to evaluate synergistic effects of (1) baseline anemia and Hb drop ≤24 hours and (2) baseline CKD and contrast load.[10] A stepwise Cox regression analysis including all variables from Tables 1 and 2 exhibiting $P<0.10$ in the Cox univariable analysis was used to determine the predictive factors of long-term mortality in patients who survived the first 30 days after TAVI (landmark analysis). For the purpose of this

Table 2. Perioperative Results for Patients With and Without AKI After TAVI

	No AKI (n=89)	AKI (n=206)	*P* Value
Intraoperative or ≤24 h			
Access strategy, no (%)			
Transfemoral	561 (71)	130 (63)	0.002
Transapical	210 (27)	67 (33)	
Transsubclavian	18 (2)	6 (3)	
Transaortic	0	3 (2)	
Circulatory support, no (%)	20 (3)	9 (4)	0.16
Prosthesis size, mm, no (%)*			
20, 23, 26	517 (66)	146 (71)	0.12
29, 31	272 (34)	59 (29)	0.12
Any complication leading to severe sustained hypotension, no (%)	24 (3)	8 (4)	0.54
Life-threatening arrhythmia, no (%)	29 (4)	10 (5)	0.44
Postimplantation balloon dilation, no (%)	130 (16)	39 (19)	0.41
Contrast volume, mL, mean±SD	142±97	158±96	0.052
Duration of procedure, min, mean±SD	99 (70–156)	105 (70–173)	0.32
Major vascular complication, no (%)	55 (7)	26 (13)	0.008
Bleeding complication, no (%)			
Life threatening or major, no (%)	104 (13)	37 (18)	0.080
Life threatening	39 (5)	15 (7)	0.19
RBC transfusion, no (%)			
None	632 (80)	133 (64)	<0.001
1–2 units	137 (17)	54 (26)	
3–4 units	14 (2)	11 (5)	
≥5 units	6 (1)	8 (4)	
Hemoglobin drop—uncorrected for RBC TF, g/dL, mean±SD	2.3±4.1	2.3±1.7	0.94
Hemoglobin drop—corrected for RBC TF, g/dL, mean±SD	2.7±4.3	3.2±2.7	0.12
Postoperative ≤72 h			
Serum creatinine (μmol/L), median (IQR)			
Preprocedural	99 (81–126)	106 (80–139)	0.12
Postprocedural	83 (67–106)	172 (122–229)	<0.001
Creatinine clearance (mL/min), mean±SD			
Preprocedural	48±20	50±27	0.49
Postprocedural	63±37	33±29	<0.001
Leucocyte count ($\times 10^9$ cells/L), mean±SD			
Preprocedural	7.3±2.2	7.2±2.1	0.55
Postprocedural	11.7±4.8	13.0±4.9	0.001
Hemoglobin (g/dL), mean±SD			
Preprocedural	12.2±4.2	12.0±1.7	0.42
Postprocedural	9.4±1.5	9.1±1.5	0.011
RBC transfusion, no (%)			
None	515 (65)	98 (48)	<0.001
1–2 units	209 (27)	63 (31)	
3–4 units	49 (6)	28 (14)	
≥5 units	16 (2)	17 (8)	
In-hospital			
Echocardiography			
Peak gradient, mean±SD	19±11	19±12	0.99
Mitral regurgitation grade ≥III, no (%)	62 (9)	10 (6)	0.21
Aortic regurgitation grade ≥III, no (%)	40 (6)	10 (5)	0.96
Length of stay (days), median (IQR)	10 (6–14)	13 (8–22)	<0.001
Mortality			
≤30 days	28 (4)	30 (15)	<0.001
≤30 days cardiac	14 (2)	17 (8)	<0.001
>30 days†	140 (18)	59 (34)	<0.001
>30 days cardiac†‡	61 (8)	26 (15)	<0.001

(Continued)

Table 2. (Continued).

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; RBC, red blood cell; TF transfusion.

*One patient did not receive a valve due to aborted TAVI after failed introduction of 18F sheath.

†N=937 patients survived >30 days after TAVI of which 199 patients died at a median of 12 (IQR: 4–23) months after TAVI.

‡The cause of death was missing or unknown in 27 of the 199 deaths (14%; n=8 in AKI group, n=19 in no AKI group).

study, RBC transfusion was forced into the multivariable analyses for predictors of AKI, whereas both RBC transfusion and AKI were forced into the multivariable analyses of 30-day and late mortality, irrespective of the *P* value obtained from the univariable analyses. Variables included in the multivariable model for the prediction of AKI, 30-day mortality, and long-term mortality are listed in online-only Data Supplement. Results are reported as adjusted OR or hazard ratio (HR) with a 95% CI. 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. Patients lost to follow-up (1.6%) were considered at risk until the date of last contact, at which point they were censored. A 2-sided $P<0.05$ was considered to indicate significance. All statistical analyses were performed with SPSS software (version 17).

Results

The baseline patient characteristics and perioperative details of the total population and of the patients with and without AKI are summarized in Tables 1 and 2, respectively. AKI occurred in 20.7% (n=206) of the patients of whom 3.1% (n=31) received renal replacement therapy. Details of AKI (stages I–III) and other changes in renal function are depicted in Figure 1. Patients with AKI had a significantly higher mortality at 30 days and during follow-up (Table 2).

Predictors of AKI

By univariable analysis, patients with AKI had a higher prevalence of congestive heart failure (66 versus 56%, *P*=0.010) and peripheral vascular disease (39 versus 28%, *P*=0.004) explaining a higher operative risk (Logistic EuroSCORE 22

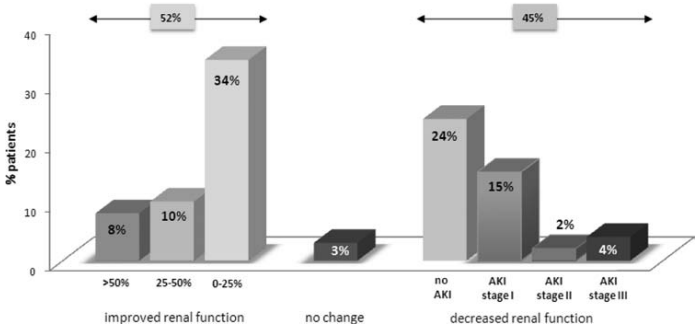


Figure 1. Changes in creatinine ≤72 hours after transcatheter aortic valve implantation.

versus 15%, *P*<0.001, Table 1). They also more often underwent transapical TAVI (33 versus 27%, *P*=0.002) and suffered more major vascular complications (13 versus 7%, *P*=0.008, Table 2). Despite the latter, there was no difference in perioperative blood loss (corrected Hb drop) between patients with and without AKI, yet patients with AKI received significantly more blood transfusions within 24 and 72 hours after TAVI. Because baseline anemia might affect the decision to administer blood transfusion, the mean Hb drop and number of blood transfusions for patients with no and with various degrees of baseline anemia was analyzed (Figure 2A–2B); patients with severe baseline anemia had 2.4 times less blood loss but on average received 2.3-fold more units of blood transfusions in comparison with patients without anemia before TAVI (*P*<0.001). Neither contrast use (*P*=0.052) nor any of the interaction terms (baseline anemia and Hb drop ≤24 hours, *P*=0.31; baseline CKD and contrast load, *P*=0.10) were significantly associated with AKI.

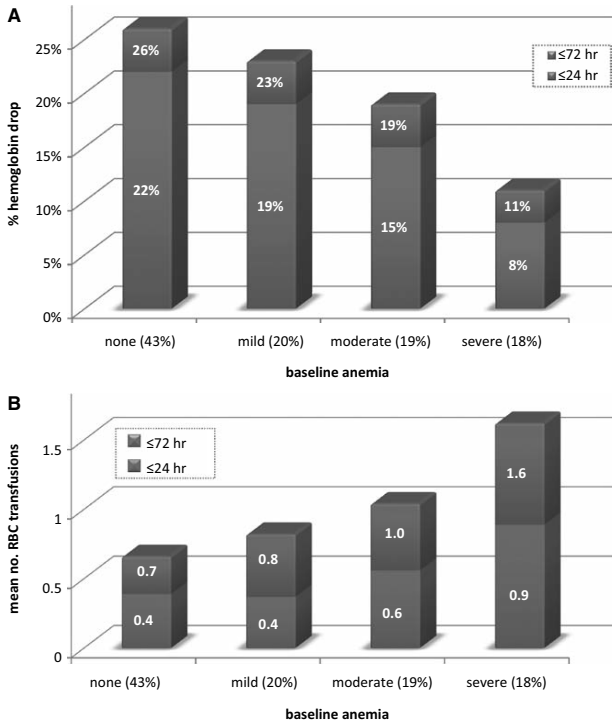


Figure 2. Mean percent Hb drop and mean number of blood transfusions ≤24 and ≤72 hours after transcatheter aortic valve implantation (TAVI) grouped according to various degrees of baseline anemia. Baseline anemia was defined as Hb <13 g/dL in men and <12 g/dL in women[23]; mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia <10.80 g/dL in men and <10.23 g/dL in women. Hb indicates hemoglobin. **A**, Mean percent Hb drop ≤24 and ≤72 hours after TAVI. Percent Hb drop ≤24 h=(baseline Hb–nadir Hb ≤24 h)/(baseline Hb); Percent Hb drop ≤72 h=(baseline Hb–nadir Hb ≤72 hours)/(baseline Hb). **B**, Mean number of blood transfusions ≤24 and ≤72 hours after TAVI. AKI indicates acute kidney injury.

Table 3. Independent Predictors of AKI After TAVI

Variable	OR (95% CI)	*P* Value
RBC transfusion ≤24 h		
None	Reference	0.003
1–2 units	1.47 (0.98–2.22)	0.064
3–4 units	3.05 (1.24–7.53)	0.015
≥5 units	4.81 (1.45–15.95)	0.010
Peripheral vascular disease	1.48 (1.05–2.10)	0.026
Congestive heart failure	1.43 (1.01–2.03)	0.042
Maximum leucocyte count ≤72 h (per 10^9 cells/L increase)	1.05 (1.02–1.09)	0.001
Logistic EuroSCORE (per % increase)	1.02 (1.00–1.03)	0.006

AKI indicates acute kidney injury; TAVI, transcatheter aortic valve implantation; RBC, red blood cell.

In a descending order of the magnitude of the OR, we found by multivariable analysis that the number of units of blood transfusion ≤24 hours was the strongest predictor of AKI (≥5 units, OR, 4.81 [1.45–15.95]; 3–4 units, OR, 3.05 [1.24–7.53]; 1–2 units, OR, 1.47 [0.98–2.22]), followed by peripheral vascular disease (OR, 1.48 [1.05–2.10]), congestive heart failure (OR, 1.43 [1.01–2.03]), leucocyte count ≤72 hours after TAVI (OR, 1.05 [1.02–1.09]), and Logistic EuroSCORE (OR, 1.02 [1.00–1.03]). Potential triggers of blood transfusion such as baseline anemia, bleeding-vascular complications, and perioperative blood loss (corrected Hb drop) were not identified as independent predictors of AKI (Table 3).

Prognostic Implications

Independent predictors of 30-day mortality consisted of perioperative life-threatening bleeding (OR, 6.65 [2.28–19.44]), aortic regurgitation post-TAVI (OR, 4.80 [1.78–12.96]), AKI (OR, 3.15 [1.56–6.38]), leucocyte count ≤72 hours (OR, 1.13 [1.06–1.20]), and Logistic EuroSCORE (OR, 1.04 [1.02–1.06], Table 4). Mortality during follow-up in patients who survived the first 30 days was determined by a mix of patient-related variables and by the administration of blood transfusion for ≤72 hours (≥5 units, HR, 2.54 [1.34–4.81], 3–4 units, HR, 2.03 [1.26–3.24], 1–2 units, HR, 1.32 [0.94–1.86]) in addition to AKI (HR, 1.57 [1.13–2.17], Table 5). Kaplan–Meier survival estimates for increasing severity of AKI, baseline anemia, and number of transfusions are shown in Figure 3.

Table 4. Independent Predictors of Mortality ≤30 Days After Transcatheter Aortic Valve Implantation

Variable	OR (95% CI)	*P* Value
Life-threatening bleeding	6.65 (2.28–19.44)	0.001
Post operative aortic regurgitation grade ≥III	4.80 (1.78–12.96)	0.002
Acute kidney injury	3.15 (1.56–6.38)	0.001
Maximum leucocyte count ≤72 h (per 10^9 cells/L increase)	1.13 (1.06–1.20)	<0.001
Logistic EuroSCORE (per % increase)	1.04 (1.02–1.06)	<0.001
RBC transfusion ≤24 h		
None	Reference	0.72
1–2 units	0.76 (0.33–1.75)	0.51
3–4 units	0.31 (0.03–3.06)	0.31
≥5 units	1.01 (0.15–6.73)	0.99

Table 5. Independent Predictors of Mortality >30 Days After Transcatheter Aortic Valve Implantation

Variable	HR (95% CI)	*P* Value
RBC transfusion ≤72 h		
None	Reference	0.004
1–2 units	1.32 (0.94–1.86)	0.11
3–4 units	2.03 (1.26–3.24)	0.003
≥5 units	2.54 (1.34–4.81)	0.004
Baseline anemia		
None	Reference	0.005
Mild	0.85 (0.54–1.34)	0.48
Moderate	1.49 (1.01–2.20)	0.043
Severe	1.75 (1.18–2.60)	0.005
Acute kidney injury	1.57 (1.13–2.17)	0.007
Peripheral vascular disease	1.69 (1.25–2.30)	0.001
Congestive heart failure	1.62 (1.16–2.26)	0.004
Male sex	1.53 (1.14–2.06)	0.005
Atrial fibrillation	1.46 (1.06–1.99)	0.019

RBC denotes red blood cell.

Discussion

In this multicenter study including 995 patients who underwent TAVI we found that AKI occurred in 21% of the patients and that the number of perioperative blood transfusions was the strongest predictor of AKI but not the clinical indications of transfusion (ie, baseline anemia, perioperative vascular-bleeding complications, or blood loss). AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality.

The frequency of AKI after TAVI has been reported to vary between 12% and 57% in previous but smaller series of patients using various definitions of AKI.[2–10] The herein reported point estimate of 21% most likely reflects the incidence of AKI encountered in clinical practice, given the sample size and the multicenter nature of this study. Irrespective of the true value, AKI poses a clinical problem as it is associated with an increased mortality at 30 days and beyond. This has also been shown by others and suggests that the outcome of TAVI may be improved by—among others—implementing all measures to prevent AKI.[5–10]

For that purpose it is essential to understand the pathophysiologic mechanism(s) of AKI after TAVI. Unfortunately, a clinical study such as this one cannot do so, yet the analysis of the association between AKI and patient- and procedure-related variables that are readily available (eg, patient demographics) or subject to change or improvement (eg, execution of procedure) may be helpful.

With respect to execution of the procedure, the findings of this study indicate that AKI and, therefore, outcome may be improved by a more careful use of blood transfusions. As mentioned, the number of blood transfusions was found

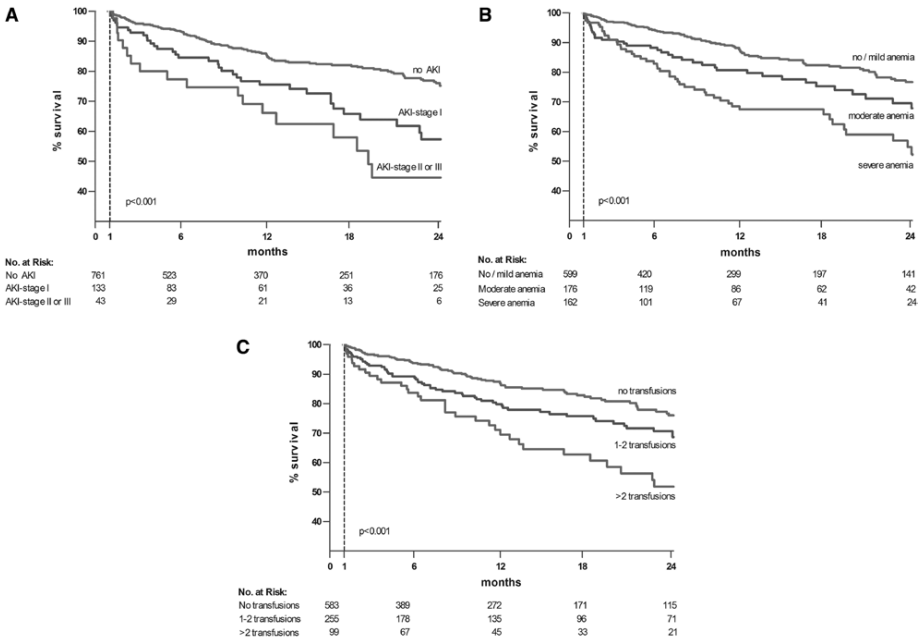


Figure 3. Time-to-event curves for selected risk factors in patients who survived the first 30 days after transcatheter aortic valve implantation (TAVI) (landmark analysis). Event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test. **A**, Time-to-event curves for patients without acute kidney injury (AKI), AKI-stage I and with AKI-stage II or III after TAVI. **B**, Time-to-event curves for patients without transfusions, 1–2 transfusions and with >2 transfusions ≤72 h after TAVI. **C**, Time-to-event curves for patients with no and various degrees of baseline anemia. Baseline anemia was defined as Hb <13 g/dL in men and <12 g/dL in women[23]; mild anemia 12.0 to 12.99 g/dL in men and 11.30 to 11.99 g/dL in women, moderate anemia 10.80 to 11.99 g/dL in men and 10.23 to 11.29 g/dL in women, and severe anemia <10.80 g/dL in men and <10.23 g/dL in women. Hb indicates hemoglobin.

to be the strongest predictor of AKI with a distinct gradient of risk. The relation between AKI and transfusion is consistent with other reports that studied patients who underwent TAVI or cardiac surgery,[5,6,10,26,27] yet, such a strong relationship between AKI and the number of transfusions has not been reported. Noteworthy, we also found that the clinical triggers upon which one may decide to administer blood during TAVI were not associated with AKI. If true, this suggests that one should be more restrictive in the use of blood transfusions during TAVI and that the need of unequivocal criteria for the decision of blood transfusion is advocated. This is illustrated by the findings that patients without anemia had a 2.4 times greater Hb drop in comparison with patients with severe baseline anemia. This may be explained by a different patient and procedure planning in addition to differences in the execution of TAVI (ie, control of hemostasis) in patients with different baseline risks. Interventions that reduce perioperative transfusions may protect against AKI, especially in anemic patients.[27]

The absence of a relationship between AKI and the indications for transfusion in addition to the fact that we did not find a relationship between AKI and periprocedural complications leading to hypotension supports a direct harmful effect of transfusion on the kidneys. It is known that preserved RBCs suffer structural or functional changes including reduced deformability and increased aggregability, all of which—particularly in older patients with impaired renal function—might induce (further) renal dysfunction.[28] Also the coadministration of proinflammatory molecules may play a role either directly or indirectly by inducing inflammation.[29] This may explain the relation found in this and other studies between postoperative leucocyte count and AKI.[4,6,10,30]

At variance with percutaneous coronary intervention (PCI),[31] we found a borderline association between contrast load and AKI in the univariable analysis, yet contrast load was not found to be an independent predictor. The absence of an association cannot be explained by a restrictive use of contrast in the present population considering the mean values and standard deviations (142±97 and 158±96 mL) although this may be an issue of sample size as a result of which a significant statistical difference was not detected. The current findings suggest that unlike PCI, contrast has only a minor effect on the development of AKI in patients who undergo TAVI.

With respect to the patient-related variables and, thus, patient selection, it is unlikely that we will exclude patients with peripheral vascular disease because TAVI was specifically developed for patients who are too high a risk for aortic

valve replacement. These patients often have widespread atherosclerosis including the peripheral circulation. It remains to be seen how additional pre- and postoperative care may avoid AKI such as optimal perioperative hydration.

Apart from perioperative blood transfusion and AKI, we found a number of other predictors of early and late mortality after TAVI. In accordance with previous series, we found severe bleeding and postoperative aortic regurgitation to be associated with a 5-fold increased risk of early death,[32] whereas severe baseline anemia, peripheral vascular disease, heart failure, male sex, and atrial fibrillation were independent predictors of late death.[12,33,34] These findings confirm the importance of appropriate patient selection to improve outcome after TAVI.

Limitations

This multicenter observational assessment in a large series of patients may estimate the frequency of AKI and its predictors but it cannot elucidate the precise pathophysiologic mechanism(s). This is needed to propose in greater detail improvements in patient and procedure planning and execution in addition to eventual changes in postoperative care. We also acknowledge the formulation of the research question during and after the data collection and the absence of a prespecified case report form. As a result, despite a high degree of completeness (online-only Data Supplement), the timing of the collection of the individual variables may not be consistent, which may affect the precision of the current findings. In addition, there was no uniform protocol of blood transfusion, as a result of which we were are not able to unravel the true triggers of transfusion, thereby precluding specific propositions of improvement.

Conclusions

AKI occurred in 21% of the patients after TAVI. The number of blood transfusions, but not the indication of transfusion, predicted AKI. AKI was a predictor of both short- and long-term mortality, whereas blood transfusion predicted long-term mortality. These findings indicate that the outcome of TAVI may be improved by a more restrictive use of blood transfusions.

Disclosures

Dr Rodés-Cabau is a consultant for and received funding from Edwards Lifesciences Inc; Drs Kefer and van Garsse are physician proctors for Edwards Lifesciences Inc; Drs Bosmans and de Jaegere are physician proctors for Medtronic CoreValve Inc, MN.

References

1. Buellesfeld L, Windecker S. Transcatheter aortic valve implantation: the evidence is catching up with reality. *Eur Heart J*. 2011;32:133–137.
2. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607.
3. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187–2198.
4. Aregger F, Wenaweser P, Hellige GJ, Kadner A, Carrel T, Windecker S, Frey FJ. Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. *Nephrol Dial Transplant*. 2009;24:2175–2179.
5. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochellière R, Doyle D, Masson JB, Gutiérrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodés-Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. *Eur Heart J*. 2010;31:865–874.
6. Nuis RJ, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv*. 2011;77:881–889.
7. Sinning JM, Ghanem A, Steinhäuser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2010;3:1141–1149.
8. Elhmidi Y, Bleiziffer S, Piazza N, Hutter A, Opitz A, Hettich I, Kornek M, Ruge H, Brockmann G, Mazzitelli D, Lange R. Incidence and predictors of acute kidney injury in patients undergoing transcatheter aortic valve implantation. *Am Heart J*. 2011;161:735–739.
9. Strauch JT, Scherner MP, Haldenwang PL, Pfister R, Kuhn EW, Madershahian N, Rahmanian P, Wippermann J, Wahlers T. Minimally invasive transapical aortic valve implantation and the risk of acute kidney injury. *Ann Thorac Surg*. 2010;89:465–470.
10. Van Linden A, Kempfert J, Rastan AJ, Holzhey D, Blumenstein J, Schuler G, Mohr FW, Walther T. Risk of acute kidney injury after minimally invasive transapical aortic valve implantation in 270 patients. *Eur J Cardiothorac Surg*. 2011;39:835–42; discussion 842.
11. Butler CE, Dickens EL. Transfusion tomorrow: Royal College of Pathologists, November 2010. *Transfus Med*. 2011;21:224–230.
12. Van Mieghem NM, Nuis RJ, Tzikas A, Piazza N, Schultz C, Serruys PW, de Jaegere PP. Prevalence and prognostic implications of baseline anaemia in patients undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2011;7:184–191.
13. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B, Cribier A, De Jaegere P, Fournial G, Kappetein AP, Kovac J, Ludgate S, Maisano F, Moat N, Mohr F, Nataf P, Piérard L, Pomar JL, Schofer J, Tornos P, Tuzcu M, van Hout B, Von Segesser LK, Walther T; European Association of Cardio-Thoracic Surgery; European Society of Cardiology; European Association of Percutaneous Cardiovascular Interventions. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2008;29:1463–1470.
14. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol*. 2006;47:1214–1223.
15. Webb JG, Chandavimol M, Thompson CR, Ricci DR, Carere RG, Munt BI, Buller CE, Pasupati S, Lichtenstein S. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation*. 2006;113:842–850.
16. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation*. 2007;116(11 Suppl):I240–I245.
17. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, Maisano F, Ramondo A, Ussia GP, Ettori F, Poli A, Brambilla N, Saia F, De Marco F, Colombo A. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. *Circ Cardiovasc Interv*. 2010;3:359–366.
18. Bapat V, Khawaja MZ, Attia R, Narayana A, Wilson K, Macgillivray K, Young C, Hancock J, Redwood S, Thomas M. Transaortic Transcatheter Aortic valve implantation using Edwards Sapien valve: a novel approach. *Catheter Cardiovasc Interv*. 2012;79:733–740.
19. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253–269.

20. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
21. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1–S266.
22. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW; American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108:2154 2169.
23. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5–37 mmentReference13/
24. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. The EPILOG Investigators. *N Engl J Med*. 1997;336:1689–1696.
25. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. 1987;82:703–713.
26. Karkouti K, Wijeysundera DN, Yau TM, Callum JL, Cheng DC, Crowther M, Dupuis JY, Fremes SE, Kent B, Laflamme C, Lamy A, Legare JF, Mazer CD, McCluskey SA, Rubens FD, Sawchuk C, Beattie WS. Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation*. 2009;119:495–502.
27. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, Beattie WS. Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. *Anesthesiology*. 2011;115:523–530.
28. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, Starr NJ, Blackstone EH. Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med*. 2006;34:1608–1616.
29. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation*. 2007;116:2544–2552.
30. Sinning JM, Scheer AC, Adenauer V, Ghanem A, Hammerstingl C, Schueler R, Müller C, Vasa-Nicotera M, Grube E, Nickenig G, Werner N. Systemic inflammatory response syndrome predicts increased mortality in patients after transcatheter aortic valve implantation. *Eur Heart J*. 2012;33:1459–1468.
31. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*. 2002;105:2259–2264.
32. Ussia GP, Barbanti M, Petronio AS, Tarantini G, Ettori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De Carlo M, Napodano M, Fiorina C, De Marco F, Antoniucci D, de Cillis E, Capodanno D, Tamburino C; CoreValve Italian Registry Investigators. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J*. 2012;33:969–976.
33. Hayashida K, Morice MC, Chevalier B, Hovasse T, Romano M, Garot P, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B, Lefèvre T. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. *J Am Coll Cardiol*. 2012;59:566–571.
34. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, Khattab AA, Meuli F, Roth N, Eberle B, Erdös G, Brinks H, Kalesan B, Meier B, Jüni P, Carrel T, Windecker S. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol*. 2011;58:2151–2162.

PART 5

EFFECTS OF PRE-OPERATIVE ANEMIA AND BLOOD TRANSFUSIONS

CHAPTER 12

Prevalence and effects of pre-operative anemia on short- and long-term mortality in patients undergoing transcatheter aortic valve implantation

ABSTRACT

Background - There is scant information on the prevalence of pre-operative anemia in patients undergoing transcatheter aortic valve implantation (TAVI) and whether it is an independent predictor of mortality. This study sought to determine the prevalence of pre-operative anemia and the effects of the various levels of pre-operative hemoglobin (Hb) on short- and long-term mortality in patients undergoing TAVI.

Methods and Results - 10-center observational study encompassing 1599 patients with aortic stenosis who underwent TAVI. Pre-operative anemia was defined by the World Health Organization criteria (Hb <12.0 in women and <13.0 g/dL in men). Uni- and multivariable analyses were performed to assess the association between preoperative anemia and various Hb levels, and all-cause mortality (30 days, 1 year median follow-up).

The prevalence of preoperative anemia was 57% with a mean pre-operative Hb concentration of 12.1 ± 1.7 g/dL. Independent determinants of preoperative anemia were the following dichotomous patient-related variables (descending order of OR [95% CI]): pre-operative mitral regurgitation grade≥III (1.80 [1.28 -2.52]), history of heart failure (1.74 [1.41-2.16]), diabetes (1.47 [1.14-1.88]), male gender (1.46 [1.16-1.85]) and peripheral vascular disease (1.36 [1.07-1.73]). Body mass index was inversely associated with preoperative anemia (0.29 [0.16-0.51]). Postoperative aortic regurgitation grade≥III was the most dominant (OR [95%CI]) independent predictor of 30-day mortality (4.64 [1.89-11.43]) while preoperative anemia was associated with an OR (95%CI) of 1.89 (1.04-3.46). Yet, the severity of preoperative anemia was the strongest independent predictor of mortality during follow-up; HR (95% CI) was 2.38 (1.37-4.13) in patients with Hb 10-11 g/dl and 2.92 (1.66-5.13) in patients with Hb <10 g/dl. Patients with anemia received 2 times more often≥1 blood transfusion in comparison to patients without anemia. Blood transfusion independently predicted mortality at 30 days and follow-up; per unit of transfusion the risk of death

increased by 20% (95% CI: 4-39%) at 30 days and with 13% (95% CI: 6-21%) during follow-up.

Conclusions - Preoperative anemia is prevalent in more than half of patients undergoing TAVI. Notwithstanding differences in baseline characteristics, preoperative anemia independently predicted 30-day and late mortality. The need for blood transfusion was associated with worse outcome.

Keywords: Transcatheter aortic valve implantation; anemia; hemoglobin; blood transfusion; predictors

Introduction

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered at high risk for surgical valve replacement (AVR)[1-2]. These patients, therefore, often have pre-existing comorbid conditions that may affect outcome offsetting treatment effects.

Anemia is a common finding in (elderly) patients and has been shown to be an independent risk factor for early and/or late mortality in the general and elderly population[3-4], in patients with coronary artery disease including acute coronary syndrome[5] and heart failure[6] and in patients undergoing percutaneous and surgical cardiac interventions[7-10].

In a recent study including 118 patients who underwent TAVI, pre-operative anemia was seen in half of the patients and was associated with increased 1-year mortality[11]. Yet, the relationship between the degree of pre-operative anemia and the impact of confounders due to differences in baseline risk between patients with and without anemia on outcome need further elucidation. This information may be helpful since measures aimed at correcting or treating anemia and its cause may conceptually improve operative outcome[12].

We, therefore, sought to determine the prevalence of pre-operative anemia and the effects of the various levels of pre-operative hemoglobin (Hb) concentration on short- and long-term mortality in a series of 1599 patients undergoing TAVI.

Methods

Study Population.

The study population stems from a cohort of 1651 patients who underwent TAVI with the Medtronic CoreValve System (MCS, Medtronic Inc, MN), the Edwards SAPIEN or SAPIEN XT Valve (ESV, Edwards Lifesciences, Irvine, CA) or the Direct Flow Valve (DFV, Direct Flow Medical, Inc) from November 2005 to August 2012 in the following institutions:

1) Quebec Heart and Lung Institute, Canada (n=287); 2) Rotterdam Thoraxcenter, Netherlands (n=267); 3) University Hospital Bonn, Germany (n=255); 4) Bergmannsheil, Ruhr-University Bochum, Germany (n=202); 5) University Hospital Maastricht, Netherlands (n=145); 6) University Hospital Saint-Luc, Belgium (n=122); 7) University Hospital Antwerp, Belgium (n=120); 8) Angiografia de Occidente, Colombia (n=93); 9) Royal Perth Hospital, Australia (n=90); 10) Hospital Clínico Universitario de Valladolid, Spain (n=70).
Patients with missing baseline Hb values (n=9), and patients on chronic hemodialysis (n=43) were excluded from analyses because anemia in the latter group is most likely a marker of the severity of illness[9]. The final study population, therefore, consists of 1599 patients.

In accordance with the institutions policies, every patient gave written informed consent for TAVI and the use of anonymous clinical, procedural and follow-up data for research in accordance with Institutional Review Board approval.

Procedure.

Planning and execution of TAVI have been described before[13]. All procedures were performed under local or general anesthesia using the MCS (valve sizes 23, 26, 29, 31 mm), ESV (valve size 23, 26, 29 mm) or DFV (valve size 24, 25 mm). After TAVI, antiplatelet therapy consisted of clopidogrel 75 mg for 6 months and aspirin 80-100 mg indefinitely. Patients on oral anticoagulant therapy before TAVI received peri-procedural therapeutic anticoagulation with unfractionated heparin or low molecular weight heparin in combination with either clopidogrel or aspirin. Oral anticoagulation was resumed shortly after TAVI.

Definitions And Data Collection.

In each hospital, blood samples for hematology and chemistry were taken before and at fixed intervals up to 72 hrs after TAVI and included the nadir Hb concentration, maximum

serum creatinine (SCr) and maximum leucocyte count. Pre-operative anemia was defined according to the American College of Physicians and World Health Organization criteria as a preoperative Hb level <12.0 g/dl in women and <13.0 g/dl in men[14]. Patients were also divided into categories of 1.0-g/dL Hb increments from <10.0 to ≥15 g/dL to assess the dose-dependent effects of decreased versus normal pre-operative Hb level on mortality.

Pre-operative SCr values were used to calculate the baseline SCr clearance using the Cockcroft and Gault equation[15]. In accordance with the K/DOQI guidelines, pre-operative kidney function was classified as stage I (>90 ml/min/1.73 m^2), stage II (60-89 ml/min/1.73 m^2), stage III (30-59 ml/min/1.73 m^2), stage IV (15-29 ml/min/1.73 m^2) and stage V (<15 ml/min/1.73 m^2), with stage ≥ II indicating chronic kidney disease (CKD)[16].

After TAVI, the nadir Hb concentration was determined≤ 24 and ≤72 hrs after TAVI and used to define the Hb decline relative to the patient's pre-operative Hb value. The number of units of blood transfusions was determined at 3 time intervals: ≤24, >24 to ≤72 hrs, and >72 hrs of TAVI. All endpoints were defined according to the Valve Academic Research Consortium (VARC) recommendations[17].

Follow-Up.

Follow-up data on patient mortality were collected from the civil registries or the referring physician or general practitioner and was complete for all of the patients at 30 days and for 99.2% at follow-up (median of 356 (IQR: 89-662) days). Of all 398 patients who died during follow-up, the cause of death was confirmed in 88.9%, unknown in 6.5% and missing/not assessed in 4.5%. The cause of death grouped according to the presence of pre-operative anemia are listed in **Supplement A** and classified as cardiovascular or non-cardiovascular in accordance with the VARC criteria[17].

Statistical Analysis.

Details of data completeness and management are summarized in **Supplement B**. Categorical variables are summarized as frequencies and percentages and were compared with the Chi square test or Fisher's exact test. The Shapiro-Wilk test was used to test for a normal distribution of continuous variables and comparison of continuous variables was done by using the Student's t tests or Wilcoxon's rank-sum test when appropriate. The independent determinants of pre-operative anemia were assessed using forward stepwise logistic regression analyses including all variables from Table 1 with $p<0.10$ in the univariable analysis. Independent determinants of 30-day and cumulative late mortality were assessed by, respectively, forward stepwise logistic and Cox regression analyses including all variables from Table 1 and 2 with $p<0.10$ in the univariable analyses. Exception was made for aortic regurgitation post TAVI which was forced into the multivariable model independent of the p-value (which proved to be 0.12) given its established predictive effect on late mortality[18-23]. The impact of low pre-operative Hb level on outcome was assessed by forcing this variable into the model of 30-day and late mortality both as a continuous and a dichotomous variable (anemia). This was also done for Hb coded as a multi-category predictor in 1-g/dL increments, with the Hb category exhibiting the lowest event rate used as the reference group[5]. Interaction terms were tested to evaluate the potential additive and/or synergistic harmful effects of baseline anemia and Hb decline at $\leq$24 and $\leq$72 hr after TAVI. Variables included in the multivariable model of determinants of pre-operative anemia, 30-day mortality and late mortality are listed in **Supplement C.** Results are reported as adjusted odds ratio (OR) or hazard ratio (HR) with a 95% confidence interval (CI). Kaplan-Meier methods were used to illustrate the timing of events during follow-up; statistical assessment was performed by the log-rank test. Patients lost to follow-up (0.8%) were considered at risk until the date of

last contact at which point they were censored. A two-sided p<0.05 was considered to indicate significance and all statistical analyses were performed with SPSS software version 20.0.

Table 1. Baseline characteristics of patients undergoing transcatheter aortic valve implantation grouped according to the presence of pre-operative anemia

	Entire cohort n = 1599	No anemia n = 693	Anemia n = 906	p-value
Age (yrs), mean ± SD	81 ± 9	80 ± 7	81 ± 7	<0.001
Male, n (%)	830 (52)	330 (48)	500 (55)	0.003
Height (cm), mean ± SD	165 ± 9	166 ± 9	164 ± 10	0.026
Weight (kg), mean ± SD	72 ± 15	74 ± 15	71 ± 14	0.001
Body mass index (kg/m2), mean ± SD	26.5 ± 4.8	26.9 ± 5.0	26.4 ± 4.7	0.033
Body surface area (m2), mean ± SD	1.81 ± 0.21	1.83 ± 0.22	1.80 ± 0.20	0.001
New York Heart Association class ≥ III, n (%)	1338 (84)	559 (81)	779 (86)	0.004
Previous cerebrovascular event, n (%)	294 (18)	116 (17)	178 (20)	0.14
Previous myocardial infarction, n (%)	414 (26)	166 (24)	248 (28)	0.12
Previous coronary artery bypass graft surgery, n (%)	396 (25)	180 (26)	216 (24)	0.33
Previous percutaneous coronary intervention, n (%)	507 (32)	202 (29)	305 (34)	0.057
History of heart failure, n (%)	909 (57)	325 (47)	584 (65)	<0.001
Diabetes mellitus, n (%)	451 (28)	178 (26)	273 (30)	0.050
Hypertension, n (%)	1234 (77)	534 (77)	700 (77)	0.92
Peripheral vascular disease, n (%)	437 (27)	157 (23)	280 (31)	<0.001
Chronic obstructive pulmonary disease, n (%)	453 (28)	193 (28)	260 (29)	0.71
Creatinine (umol/L), median (IQR)	98 (79-123)	93 (77-114)	103 (82-132)	<0.001
Creatinine clearance (ml/min), mean ± SD	51 ± 22	55 ± 21	48 ± 21	<0.001
Creatinine clearance (ml/min/1.73 m2), n (%)				
stage I (>90)	78 (5)	43 (6)	35 (4)	
stage II (60-89)	361 (23)	194 (28)	167 (19)	
stage III (30-59)	940 (59)	390 (56)	550 (61)	<0.001
stage IV (15-29)	198 (12)	59 (9)	139 (15)	
stage V (<15)	16 (1)	5 (1)	11 (1)	
Hemoglobin (g/dl), mean ± SD	12.1 ± 1.7	13.6 ± 1.0	11.0 ± 1.1	<0.001
Leucocyte count (x 10^9/l), mean ± SD	7.3 ± 2.2	7.4 ± 2.0	7.2 ± 2.3	0.037
Atrial fibrillation, n (%)	453 (28)	178 (26)	275 (30)	0.040
Permanent pacemaker, n (%)	204 (13)	78 (11)	126 (14)	0.12
Left ventricular ejection fraction, mean ± SD	52 ± 15	53 ± 14	52 ± 15	0.13
Aortic valve area (cm2), mean ± SD	0.68 ± 0.19	0.68 ± 0.19	0.68 ± 0.19	0.44
Peak gradient, mean ± SD	72 ± 25	72 ± 23	72 ± 25	0.80
Mitral regurgitation grade ≥ III, n (%)	203 (13)	61 (9)	142 (16)	<0.001
Aortic regurgitation grade ≥ III, n (%)	120 (8)	46 (7)	74 (8)	0.25
Logistic Euroscore, median (IQR)	19.3 (11.6-30.7	17.4 (10.3-26.4)	20.9 (12.7-33.0)	<0.001

Results

Baseline patient characteristics and operative details of the 1599 patients are summarized in **Table 1 and 2**. Patients with anemia were older (81 vs. 80 years, p<0.001), more frequently male (55 vs. 48%, p=0.003), and had a lower body mass index (26.4 vs. 26.9 kg/m2, p=0.033) and body surface area (1.80 vs. 1.83 m^2, p=0.001). They were also more symptomatic (NYHA class≥III: 86 vs. 81%, p=0.0 04), had more often a history of heart

failure (65 vs. 47%, p<0.001) and had a higher prevalence of peripheral vascular disease (31 vs. 23%, p<0.001), CKD (77 vs. 66%, p<0.001), atrial fibrillation (30 vs. 26%, p=0.040) and mitral regurgitation grade≥III (16 vs. 9%, p<0.001) , but showed a lower pre-operative leucocyte count (7.2 vs. 7.4 x 10^9 cells/L, p=0.037). They, therefore, had a higher estimated operative risk (Logistic EuroSCORE: 21 vs. 17%, p<0.001) as compared to patients without anemia. The baseline patient characteristics independently associated with pre-operative anemia are shown in **Table 3.**

Table 2. Peri-operative results of patients undergoing transcatheter aortic valve implantation grouped according to the presence of pre-operative anemia

	No anemia n = 693	Anemia n = 906	p-value
Intra-operative or ≤24 hr			
Early experience, n (%) *	133 (19)	184 (20)	0.58
Device, n (%)			
Medtronic CoreValve	419 (61)	527 (58)	0.37
Edwards Sapien	266 (39)	373 (41)	0.25
Direct Flow Medical	6 (1)	2 (0.2)	0.084
Access strategy, n (%)			
Trans-femoral	539 (78)	673 (74)	
Trans-apical	134 (19)	192 (21)	0.25
Trans-subclavian	12 (2)	26 (3)	
Trans-aortic	8 (1)	15 (2)	
Circulatory support, n (%)	21 (3)	25 (3)	0.75
Prosthesis size, n (%) †			
20, 23, 25-mm	147 (21)	196 (22)	0.84
26, 29, 31-mm	544 (79)	707 (78)	0.84
Post implantation balloon dilation, n (%)	94 (14)	162 (18)	0.020
Duration of procedure (min), mean ± SD	118 ± 74	111 ± 64	0.032
Hemoglobin (g/dl), mean ± SD			
Preprocedural	13.6 ± 1.0	11.0 ± 1.1	<0.001
Postprocedural	10.9 ± 1.7	9.5 ± 1.3	<0.001
Decline	2.7 ± 1.4	1.5 ± 1.4	<0.001
Blood transfusion, n (%)			
none	594 (86)	646 (71)	
1-2 units	67 (10)	205 (23)	<0.001
3-4 units	13 (2)	41 (5)	
≥ 5 units	19 (3)	14 (2)	
Post-operative ≤72 hr			
Serum creatinine (µmol/l), median (IQR)			
Preprocedural	93 (77-114)	103 (82-132)	<0.001
Postprocedural	89 (73-117)	98 (74-136)	0.003
Creatinine clearance (ml/min), mean ± SD			
Preprocedural	55 ± 21	48 ± 21	<0.001
Postprocedural	58 ± 30	54 ± 37	0.056
Leucocyte count (x 10^9/l), mean ± SD			
Preprocedural	7.4 ± 2.0	7.2 ± 2.3	0.037
Postprocedural	11.9 ± 4.2	11.7 ± 5.8	0.52
Hemoglobin (g/dl), mean ± SD			
Postprocedural	10.3 ± 1.6	9.0 ± 1.3	<0.001
Decline	3.3 ± 1.5	2.0 ± 1.3	<0.001
Blood transfusion, n (%)			
none	544 (79)	489 (54)	<0.001

1-2 units	95 (14)	286 (32)	
3-4 units	26 (4)	95 (11)	
≥ 5 units	28 (4)	36 (4)	
In-hospital results			
Echocardiography			
Peak gradient, mean ± SD	19 ± 8	18 ± 10	0.22
Mitral regurgitation grade ≥ III, n (%)	43 (7)	100 (12)	<0.001
Aortic regurgitation grade ≥ III, n (%)	35 (5)	47 (6)	0.83
Length of stay (days), median (IQR)	8 (6-14)	10 (6-15)	<0.001
In-hospital complications			
Mortality (≤ 30 days) ‡			
all-cause	34 (5)	84 (9)	0.001
cardiovascular	27 (4)	64 (7)	0.007
non-cardiovascular	7 (1)	19 (2)	0.089
Myocardial infarction (peri-procedural, ≤ 72hr)	15 (2)	10 (1)	0.090
Cerebrovascular complications			
major stroke	13 (2)	27 (3)	0.16
minor stroke	12 (2)	5 (1)	0.023
TIA	8 (1)	5 (1)	0.18
Vascular complication, n (%)			
major	57 (8)	85 (9)	0.42
minor	69 (10)	80 (9)	0.44
Bleeding complication, n (%)			
life-threatening or disabling	31 (5)	36 (4)	0.62
major	45 (7)	78 (9)	0.12
minor	51 (7)	84 (9)	0.17
Acute kidney injury, n (%)			
stage 1	86 (12)	117 (13)	0.76
stage 2	10 (1)	18 (2)	0.41
stage 3	22 (3)	41 (5)	0.17
Combined 30-day safety endpoint	120 (17)	207 (23)	0.007

* Early experience represents the first 33 patients in each center who underwent transcatheter aortic valve implantation (29)
† Six patients did not receive a valve because of death before valve insertion
‡ The cause of death was missing in one patient who died ≤ 30 days

The overall prevalence of preoperative anemia was 57% and varied between 42% and 67% in the participating hospitals. The mean pre-operative Hb concentration was 12.1 ± 1.7 g/dL (range: 7.2 - 17.5 g/dL). The distribution of pre-operative Hb concentration (including the patients excluded from analysis) is presented in **Figure 1.**

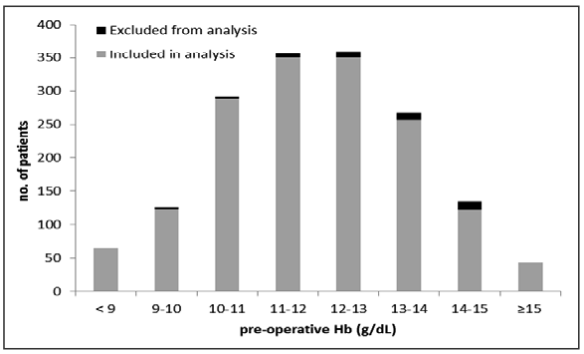


Figure 1. Distribution Of Pre-Operative Hemoglobin Concentration In Patients Undergoing Transcatheter Aortic Valve Implantation. Fourty-three patients on chronic hemodialysis were excluded from analyses because anemia in these patients is most likely a marker of the severity of illness (9).

30-day mortality.

Thirty-day all-cause mortality was 5% in patients without and 9% in patients with anemia (p=0.001). Independent predictors of 30-day all-cause mortality are shown in **Table 4.** With respect to the dichotomous variables, postoperative aortic regurgitation grade ≥III (OR: 4.64; 95% CI: 1.89-11.43) was the most powerful predictor followed by – in descending order of odds – AKI (OR: 3.03; 95% CI: 1.73-5.31), male gender (OR: 2.03; 95% CI: 1.13-3.65) and pre-operative atrial fibrillation (OR: 1.94; 95% CI: 1.11-3.38) while preoperative anemia was the weakest predictor of mortality (OR: 1.89; 95% CI: 1.04-3.46). With respect to the continuous variables, the administration of every unit of blood transfusion was associated with a 20% higher risk of 30-day mortality whereas every 1 percent increase in Logistic EuroSCORE increased the risk of death by 3%. The peak aortic valve gradient before TAVI proved to be protective.

Table 3. Multivariable logistic regression analysis for determinants of pre-operative anemia in patients undergoing transcatheter aortic valve implantation

Determinant	Odds ratio (95% CI)	p-value
Pre-operative mitral regurgitation grade ≥ III	1.80 (1.28-2.52)	0.001
History of heart failure	1.74 (1.41-2.16)	<0.001
Diabetes mellitus	1.47 (1.14-1.88)	0.003
Male gender	1.46 (1.16-1.85)	0.001
Peripheral vascular disease	1.36 (1.07-1.73)	0.013
Body surface area (per 1 m2 increase)	0.29 (0.16-0.51)	<0.001
Pre-operative creatinine (per 10 umol/L increase)	1.06 (1.04-1.09)	<0.001
Pre-operative leucocyte count (per 1 x 10^9 cells/L increase)	0.95 (0.91-1.00)	0.039
Age (per 1 year increase)	1.02 (1.01-1.04)	0.004

Late mortality.

At 1 year, all-cause mortality was 20% in patients without and 29% in patients with anemia (p<0.001); patients with anemia more frequently had a non-cardiovascular cause of death (p=0.048, **Supplement C**). The predictors of all-cause mortality during follow-up are

shown in **Table 5**. With respect to the dichotomous variables, a significant and inverse relationship was found between the severity of preoperative Hb level and mortality during follow-up. In particular patients with a preoperative Hb level <10 g/dL had a 2.92 fold higher risk of dying during the follow-up period whereas patients with a preoperative Hb level between 10-11 g/dL and 11-12 g/dL had a 2.38 and 1.88 fold high risk, respectively. Postoperative AKI (HR: 2.08; 95% CI: 1.61-2.68) and aortic regurgitation grade ≥III (HR: 1.87; 95% CI: 1.22-2.87) in addition to preoperative atrial fibrillation (HR: 1.80; 95% CI: 1.41-2.29), male gender (HR: 1.60; 95% CI: 1.26-2.04) and history of peripheral vascular disease (HR: 1.31; 95% CI: 1.01-1.69) also predicted late mortality. Similar to 30-day mortality, the administration of blood transfusions predicted mortality during follow-up; every unit of transfusion was associated with a 13% increase in risk of late death. This also accounted for leucocyte count post TAVI and Logistic EuroSCORE (i.e. 5% increase in risk of late death for every 1 percent increase in Logistic EuroSCORE) while left ventricular ejection fraction and peak gradient proved to be protective. Kaplan-Meier estimates of survival of patients without and with preoperative anemia are shown in **Figure 2.**

Table 4. Multivariable logistic regression analysis for determinants of 30-day mortality after transcatheter aortic valve implantation

Determinant	Odds ratio (95% CI)	p-value
Pre-operative anemia	1.89 (1.04-3.46)	0.038
Pre-operative hemoglobin (per 1 g/dL increase)	0.88 (0.75-1.03)	0.12
Post-operative aortic regurgitation grade ≥ III	4.64 (1.89-11.43)	0.001
Acute kidney injury, stage I-III	3.03 (1.73-5.31)	<0.001
Male gender	2.03 (1.13-3.65)	0.018
Pre-operative atrial fibrillation	1.94 (1.11-3.38)	0.019
Blood transfusion ≤24 hr (per 1 unit increase)	1.20 (1.04-1.39)	0.014
Maximum leucocyte count ≤72 hr (per 1 x 10^9 cells/L increase)	1.11 (1.06-1.17)	<0.001
Logistic EuroSCORE (per 1% increase)	1.03 (1.02-1.05)	<0.001
Pre-operative peak gradient (per 10 mmHg increase)	0.84 (0.74-0.96)	0.009

Table 5. Multivariable Cox regression analysis for determinants of cumulative late mortality after transcatheter aortic valve implantation

Determinant	Hazard ratio (95% CI)	p-value
Pre-operative anemia	1.49 (1.17-1.90)	0.001
Pre-operative hemoglobin (per g/dL increase)	0.85 (0.80-0.92)	<0.001
Pre-operative hemoglobin category, g/dL *		
≥15 vs. 14 to 15 (n=65)	1.33 (0.63-2.79)	0.45
14 to 15 (n=123)	*reference*	0.001
13 to 14 vs. 14 to 15 (n=289)	1.66 (0.96-2.88)	0.070
12 to 13 vs. 14 to 15 (n=350)	1.48 (0.85-2.58)	0.17
11 to 12 vs. 14 to 15 (n=350)	1.88 (1.09-3.25)	0.024
10 to 11 vs. 14 to 15 (n=257)	2.38 (1.37-4.13)	0.002
<10 vs. 14 to 15 (n=165)	2.92 (1.66-5.13)	<0.001
Acute kidney injury, stage I-III	2.08 (1.61-2.68)	<0.001
Post-operative aortic regurgitation grade ≥ III	1.87 (1.22-2.87)	0.004
Pre-operative atrial fibrillation	1.80 (1.41-2.29)	<0.001
Male gender	1.60 (1.26-2.04)	<0.001
Peripheral vascular disease	1.31 (1.01-1.69)	0.041
Blood transfusion ≤24 hr (per 1 unit increase)	1.13 (1.06-1.20)	<0.001
Pre-operative left ventricular ejection fraction (per 10% increase)	0.91 (0.83-0.99)	0.034
Pre-operative peak gradient (per 10 mmHg increase)	0.94 (0.90-0.99)	0.025
Maximum leucocyte count ≤72 hr (per 1 x 10^9 cells/L increase)	1.05 (1.03-1.08)	<0.001
Logistic EuroSCORE (per 1% increase)	1.01 (1.00-1.02)	0.002

* To establish the dose-dependent effect of decreased vs. normal preoperative hemoglobin values (= 14 to 15 g/dL) on cumulative late mortality, hazard ratio values of decreased hemoglobin levels are shown in steps of 1 g/dL, and each was compared with patients with hemoglobin values between 14 and 15 g/dL.

Discussion

In this multicenter study encompassing 1599 patients who underwent TAVI, we found that pre-operative anemia was present in 57% of the patients with an equal distribution of its prevalence in the participating institutions (range: 42-67%). Despite differences in baseline characteristics between patients with and without preoperative anemia, preoperative anemia was an independent predictor of 30-day and 1-year mortality (9 and 29%, respectively). Moreover, a significant inverse relationship was found between the severity of preoperative anemia (i.e. serum Hb level) and mortality during follow-up. This was in particular the case for patients with an Hb <12.0 g/dL. We also found that patients with preoperative anemia received more units of blood transfusions at 24 and 72 hrs after TAVI and that the administration of blood transfusion was an independent predictor of late mortality in a dose dependent fashion.

The herein reported prevalence of anemia of 57% is higher than demonstrated in patients with acute coronary syndrome and patients undergoing percutaneous coronary intervention or cardiac surgery (up to 36%)[5, 7-8]. This is most likely explained by differences in patient characteristics. Patients who are referred for TAVI are older and, therefore, more often have associated cardiac and non-cardiac chronic disease or comorbid conditions, which both may explain a higher prevalence of anemia in these patients[4, 24-25].

The main objective of the present study was to assess whether preoperative anemia was an independent predictor of (short- and long-term) mortality rather than being a marker of disease. For that purpose multivariable analyses were performed. With respect to 30-day mortality, preoperative anemia was an independent predictor 30-day mortality albeit with moderate strength considering its odds ratio and 95% CI. A number of postoperative complications - in particular valve dysfunction (i.e. aortic regurgitation) and renal failure – and a few baseline variables such as male gender and preoperative atrial fibrillation were more powerful independent predictors. We could not study the relationship between the severity of preoperative anemia (i.e Hb levels) and 30-day mortality due to a low absolute number of deaths in some of the Hb categories. Yet, what we perceive as an even more important clinical observation, is that patients with preoperative anemia receive more units of blood transfusion during the perioperative period and that every unit of transfusion is associated with a 20% increase in risk of 30-day mortality, which was also found in the assessment of long-term mortality albeit that the association was less pronounced (increase in risk of 13% per transfusion). In this study, the possibility of heterogeneity in timing of the collection of data in each institution precluded an accurate estimation of the total blood loss calculated by the Landefeld equation (which assumes that the net Hb decline corresponds to

the addition of the number of blood transfusion to the baseline-minus-measured post-operative nadir Hb)[26]. Yet, in accordance with our previous findings[27], the current results show that patients with anemia had a smaller post-operative Hb drop but received significant more frequent and also more units of blood transfusions as compared to patients without anemia. This suggests an uncontrolled or subjective use of blood products during TAVI. Given the significant and inverse relationship between blood transfusion and mortality, these data at least indicate that improved perioperative care (awareness) may improve outcome in addition to the need of uniform criteria for the use of blood products.

In essence, the same observations were made when studying the independent predictors of mortality during follow-up. The difference, however, was the significant inverse relationship between the severity of preoperative anemia (i.e. Hb level) and late death, in particular when the Hb level was < 12 g/dl. Preoperative anemia defined by the World Health Organization criteria was a weak independent predictor while - in descending order of hazard – AKI, postoperative aortic regurgitation, and a few baseline patient-related variables such as preoperative atrial fibrillation, male gender and peripheral vascular disease were more strongly associated with late death.

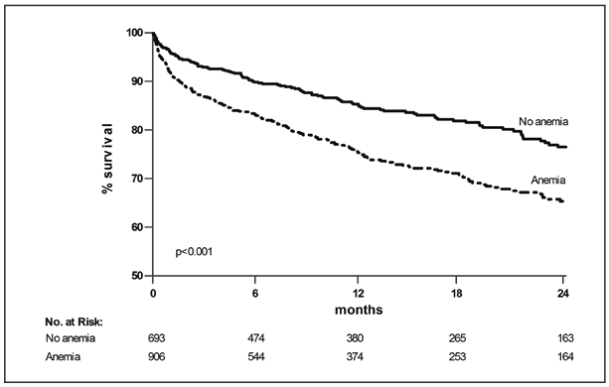


Figure 2. Kaplan-Meier Survival Estimates.

The clinical translation of the findings above is two-fold. On one hand, it is conceivable that the correction of preoperative anemia and/or treatment of its cause may beneficially affect outcome. On the other, the data of this study indicate the need of a more thoughtful use of blood transfusion during and immediately after TAVI. With respect to the former, data from surgical series indicate that common causes of anemia are chronic disease and iron deficiency anemia in addition to hospital acquired anemia[6, 12]. The first two offer a simple and logic basis for proposals of management that may improve outcome in TAVI and, potentially, other cardiac and non-cardiac interventions in patients with preoperative anemia. Its effects obviously need to be studied in appropriately designed trials. It is also clear that all efforts should be made to avoid AKI which predicted both short- and long-term mortality and aortic regurgitation which was a strong independent predictor of 30-day mortality. The latter has stimulated the design of novel frames that facilitates centring and seating of the valve within the annulus[28,29].

Limitations

Despite the fact that pre-operative anemia was an independent predictor of short- and long-term mortality by multivariable analysis, it cannot be excluded that anemia still is a marker of disease since we could not assess the cause of anemia itself. For instance, in case anemia is caused by on-going malignancy, frailty and/or malnutrition or any other treatable cause, it is conceivable that the undetermined cause of anemia is the determinant of outcome and not anemia. A similar thought also applies to blood transfusion since we did not assess the triggers why blood transfusion was administered despite the correction in the multivariable analysis for – among others - bleeding- and vascular complications. This information is needed to better understand the herein reported relation between transfusion and mortality, and to make propositions for improved peri-operative management and care.

Disclosures

Josep Rodés-Cabau is a consultant for and received funding from Edwards Lifesciences Inc.; Joelle Kefer, Leen van Garsse and Gerald Yong are physician proctors for Edwards Lifesciences Inc.; Johan Bosmans and Peter de Jaegere are physician proctors for Medtronic CoreValve Inc, MN; all other authors have nothing to declare.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.

2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, Investigators PT. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-2198.

3. Sarnak MJ, Tighiouart H, Manjunath G, MacLeod B, Griffith J, Salem D, Levey AS. Anemia as a risk factor for cardiovascular disease in The Atherosclerosis Risk in Communities (ARIC) study. *J Am Coll Cardiol*. 2002;40:27-33.

4. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA*. 1999;281:1714-1717.

5. Sabatine MS, Morrow DA, Giugliano RP, Burton PB, Murphy SA, McCabe CH, Gibson CM, Braunwald E. Association of hemoglobin levels with clinical outcomes in acute

coronary syndromes. *Circulation*. 2005;111:2042-2049.

6. Tang YD, Katz SD. Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. *Circulation*. 2006;113:2454-2461.

7. Lee PC, Kini AS, Ahsan C, Fisher E, Sharma SK. Anemia is an independent predictor of mortality after percutaneous coronary intervention. *J Am Coll Cardiol*. 2004;44:541-546.

8. Zindrou D, Taylor KM, Bagger JP. Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. *Lancet*. 2002;359:1747-1748.

9. Karkouti K, Wijeysundera DN, Beattie WS, Reducing Bleeding in Cardiac Surgery I. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation*. 2008;117:478-484.

10. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. *Am J Med*. 2004;116:58S-69S.

11. Van Mieghem NM, Nuis RJ, Tzikas A, Piazza N, Schultz C, Serruys PW, de Jaegere PP. Prevalence and prognostic implications of baseline anaemia in patients undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2011;7:184-191.

12. Karski JM, Mathieu M, Cheng D, Carroll J, Scott GJ. Etiology of preoperative anemia in patients undergoing scheduled cardiac surgery. *Can J Anaesth*. 1999;46:979-982.

13. Cribier A, Eltchaninoff H, Tron C, Bauer F, Agatiello C, Nercolini D, Tapiero S, Litzler PY, Bessou JP, Babaliaros V. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol*. 2006;47:1214-1223.

14. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.

15. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

16. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2005;67:2089-2100.

17. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *J Am Coll Cardiol*. 2011;57:253-269.

18. Gotzmann M, Lindstaedt M, Mugge A. From pressure overload to volume overload: aortic regurgitation after transcatheter aortic valve implantation. *Am Heart J*. 2012;163:903-911.

19. Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochelliere R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol*. 2010;55:1080-1090.

20. Sinning JM, Hammerstingl C, Vasa-Nicotera M, Adenauer V, Lema Cachiguango SJ, Scheer AC, Hausen S, Sedaghat A, Ghanem A, Muller C, Grube E, Nickenig G, Werner N. Aortic regurgitation index defines severity of peri-prosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2012;59:1134-1141.

21. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation*. 2007;116:I240-245.

22. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. *J Am Coll Cardiol*. 2011;58:2130-2138.

23. De Jaegere PP, Piazza N, Galema TW, Otten A, Soliman OI, Van Dalen BM, Geleijnse ML, Kappetein AP, Garcia HM, Van Es GA, Serruys PW. Early echocardiographic evaluation following percutaneous implantation with the self-expanding CoreValve Revalving System aortic valve bioprosthesis. *EuroIntervention*. 2008;4:351-357.

24. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, Khattab AA, Meuli F, Roth N, Eberle B, Erdos G, Brinks H, Kalesan B, Meier B, Juni P, Carrel T, Windecker S. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol*. 2011;58:2151-2162.

25. Nuis RJ, Dager AE, van der Boon RM, 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*. 2012;20:16-23.

26. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. 1987;82:703-713.

27. Nuis RJ, Rodes-Cabau J, Sinning JM, van Garsse L, Kefer J, Bosmans J, Dager AE, van Mieghem N, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Dumont E, van Domburg RT, de Jaegere PP. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2012;5:680-688.

28. Ribeiro H, Urena M, Kuck K, Webb J, Rodes-Cabau J. Edwards CENTERA valve. *EuroIntervention*. 2012;8:Q79-Q82

29. Nuis RJ, van Mieghem NM, van der Boon RM, van Geuns RJ, 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.

PART 6

TAVI IN LATIN AMERICA

CHAPTER 13.1

Clinical results of the Cali Colombian Medtronic CoreValve TAVI registry

Clinical Investigation

Antonio E. Dager, MD
Rutger-Jan Nuis, MSc
Bernardo Caicedo, MD
Jaime A. Fonseca, MD
Camilo Arana, MD
Lidsa Cruz, RN
Luis M. Benitez, MD
Carlos A. Nader, MD
Eduardo Duenas, MD
Eduardo J. de Marchena, MD
William W. O'Neill, MD
Peter P. de Jaegere, MD, PhD

Key words: *Aortic valve stenosis/complications/mortality/surgery; comorbidity; heart valve prosthesis implantation/methods; postoperative complications/etiology/prevention & control; registries; risk factors; treatment outcome*

From: *Department of Cardiology (Drs. Arana, Caicedo, Dager, and Fonseca, and Ms Cruz), Angiografia de Occidente, Cali, Colombia; Departments of Echocardiography (Drs. Benitez and Nader) and Cardio-Vascular Surgery (Dr. Duenas), Clinica de Occidente, Cali, Colombia; Department of Cardiology (Dr. de Jaegere and Mr. Nuis), Erasmus Medical Center, 3015 CE, Rotterdam, The Netherlands; and Cardiovascular Division (Drs. Dager, de Marchena, and O'Neill), Miller School of Medicine, University of Miami, Miami, Florida 33136*

Rutger-Jan Nuis received an ERACOL grant from the Erasmus-Columbus Latin-European exchange foundation to conduct this study.

Address for reprints:
Peter P. de Jaegere, MD, PhD, Thoraxcenter, 's-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

E-mail:
p.dejaegere@erasmusmc.nl

Colombian Experience with Transcatheter Aortic Valve Implantation of Medtronic CoreValve

At our institutions, increasing numbers of aortic stenosis patients were not candidates for surgical aortic valve replacement. Accordingly, we initiated the Cali Colombian Transcatheter Aortic Valve Implantation (TAVI) program. From March 2008 through January 2011, 53 consecutive patients (mean age, 79 ± 6 yr; men, 58%) underwent TAVI with the Medtronic CoreValve System, and data were prospectively collected. Our study's endpoints conformed with Valve Academic Research Consortium recommendations. We report our clinical results.

Predicted mortality rates were 25% (interquartile range, 17%–34%) according to logistic EuroSCORE and 6% (interquartile range, 3%–8%) according to the Society of Thoracic Surgeons score. The 30-day mortality rate was 9% (3 intraprocedural deaths, 5 total). The combined 30-day safety endpoint was 30% (major vascular sequelae, 23%; life-threatening bleeding, 12%; myocardial infarction, 4%; major stroke, 4%; and acute kidney injury [stage 3], 2%). Eight patients (15%) required post-implantation balloon dilation and 2 (4%) required valve-in-valve implantation, for a technical device success rate of 77%. Mean peak transvalvular gradient decreased from 74 ± 29 to 17 ± 8 mmHg and mean transvalvular gradient from 40 ± 17 to 8 ± 4 mmHg (both P=0.001). Moderate or severe aortic regurgitation decreased from 32% to 18% (P=0.12) and mitral regurgitation from 32% to 13% (P=0.002). The 1-year survival rate was 81%.

We found that TAVI with the CoreValve prosthesis was safe and feasible, with sustained long-term results, for treating aortic stenosis in patients at excessive surgical risk; nonetheless, serious adverse events occurred in 30% of the patients. ***(Tex Heart Inst J 2012;39(3):351-8)***

Transcatheter aortic valve implantation (TAVI) is a relatively new catheter-based, minimally invasive procedure performed on a beating heart to treat patients with aortic stenosis (AS) who are considered to be at too high a risk for surgical aortic valve replacement. The procedure has proved to be superior to medical therapy (including aortic balloon valvuloplasty) for such patients.[1] Since the first use of TAVI in 2002,[2] the number of patients thus treated has increased exponentially: an estimated 30,000 procedures had been performed by 2011, mostly in Europe and Canada.

Transcatheter aortic valve implantation is still evolving from an initially experimental therapy into an established treatment for high-risk patients with AS, and very little experience with TAVI has been reported in Latin America. At our institutions, increasing numbers of AS patients were at high surgical risk because of age or comorbidities. Therefore, we initiated the Cali Colombian TAVI program in 2007. After a nearly 3-year experience in performing TAVI with use of the Medtronic CoreValve® System (Medtronic CV Luxembourg S.a.r.l.; Luxembourg), we report our clinical results in 53 patients.

Patients and Methods

When our TAVI program was formed in November 2007, our multidisciplinary team consisted of 2 interventional cardiologists, a cardiothoracic surgeon, a vascular surgeon, an anesthetist, an imaging specialist, and 2 research nurses. The team took theoretical courses, paid multiple visits to different experienced centers in Europe, and performed 21 TAVI procedures in the presence of a proctor.

Inclusion and Exclusion Criteria

Eligibility criteria for treatment with the CoreValve have been published.[3,4] Our study's inclusion criteria were as follows: aortic valve area, ≤1 cm^2 or 0.6 cm^2/m^2; native aortic valve annular sizes, ≤20 mm or ≥27 mm; femoral artery diameter, ≥6 mm; severe symptoms (New York Heart Association [NYHA] functional class III or IV); and age ≥75 years plus a logistic EuroSCORE ≥20% or age ≥65 years with one of the following major complicating factors: liver cirrhosis, severe pulmonary disease (forced expiratory volume in 1 s, <1 L), severe pulmonary hypertension (>60 mmHg), previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular dysfunction, contraindication to open-heart surgery (previous chest radiation), or cachexia (body mass index, <18 kg/m^2).

Major exclusion criteria were life expectancy of less than 12 months because of comorbid conditions; an existing bioprosthesis; myocardial infarction within the preceding 14 days; unprotected left main coronary artery stenosis >70%; hemodynamic instability or cardiogenic shock; history of, or active, endocarditis; active peptic ulcer or upper gastrointestinal bleeding within the prior 6 months; active infections requiring current antibiotic therapy, or clinical suspicion of active infection; contraindication to antiplatelet or anticoagulative therapy or contrast media; and hypersensitivity to nitinol.

All patients underwent a structured evaluation consisting of a formal interview, physical examination, laboratory tests, 12-lead electrocardiography, transesophageal echocardiography, and angiographic evaluation of the coronary and peripheral arteries. Thirty-three of the patients also underwent this arterial study by means of multislice computed tomography.

From March 2008 through January 2011, we screened 91 consecutive patients with suspected severe AS for potential TAVI with the CoreValve. Three were referred for surgical aortic valve replacement. Fourteen continued a medical regimen without cardiac intervention: 4 by choice, 4 whose annular dimensions did not match the CoreValve criteria, 3 with nonsevere AS, 1 with unprotected left main coronary artery stenosis >70%, and 2 for unknown reasons. Of 74 patients in whom TAVI was indicated, 14 were hemodynamically unstable and needed aortic balloon valvuloplasty before TAVI. Of these 14 patients, 7 died after valvuloplasty and before TAVI could be performed, and 7 were bridged to TAVI at a median of 38 days after valvuloplasty (interquartile range [IQR], 2–57 d). In total, 21 of the 74 patients died while on the waiting list, so our study population comprised 53 patients.

Interventional Procedure

Details of the device and the procedure have been published.[4,5] In brief, the CoreValve is a trileaflet porcine pericardial tissue valve mounted on a self-expanding nitinol frame and currently available in sizes with 26- and 29-mm inflow diameters. All 53 of our patients were treated with the 3rd-generation CoreValve, which we implanted with use of an 18F disposable delivery catheter inserted into the common femoral artery or subclavian artery via a pigtail approach. We performed closure through a preclose technique with use of a Prostar® XL 10F Percutaneous Vascular Surgical System[6] (Abbott Vascular, part of Abbott Laboratories; Abbott Park, Ill), or we used surgical closure in the presence of severe circumferential femoral vascular calcification. Valve implantation was performed under fluoroscopic and angiographic guidance. We placed most patients under local anesthesia with sedation but without mechanical ventilation. Patients with a suspected increased risk of developing complications during or immediately after the procedure were placed under general anesthesia with mechanical ventilation.

Data Collection

All endpoints were selected and defined according to the Valve Academic Research Consortium (VARC) recommendations, available in 2010 and published in 2011.[7] For patients treated before 2011, we applied the VARC definitions, as other investigators have done. The VARC—consisting of representatives of academic research organizations in Europe and the United States and representatives of the European and American societies of Cardiology and Cardiothoracic Surgery—was formed in 2009. The VARC established standardized endpoint definitions for TAVI clinical trials, in order to increase comparability between studies.

Transesophageal echocardiography, including continuous pulsed-wave Doppler study, was performed at a median of 43 days before TAVI (IQR, 32–91 d) and within 7 days after TAVI, to calculate aortic valve area and mean transvalvular gradient in conformity with recommendations from the American Society of Echocardiography.[8] Paraprosthetic aortic regurgitation was determined in accordance with the following VARC-proposed criteria: jet width in central jets (percentage of left ventricular diameter), jet density, jet deceleration rate (pressure half time, ms), diastolic flow reversal in the descending aorta, and the circumferential extent of paraprosthetic aortic regurgitation.

Endpoint data collected during or immediately after the procedure included death; myocardial infarction; cerebrovascular, vascular, and bleeding sequelae; and acute kidney injury. All cerebrovascular sequelae were diagnosed by a neurologist, with evaluation of such patients daily and then at least once during a later outpatient clinical visit. Full hematologic and chemistry blood samples were collected daily from all patients during the first 3 days, to determine the severity of vascular, bleeding, and renal sequelae. The use of red blood

cell transfusions was documented by our institution's blood-bank laboratory. The occurrence of new-onset 3rd-degree atrioventricular (AV) block and the timing of permanent pacemaker implantation were recorded during the patients' hospital stays.

In conformity with VARC recommendations, technical (device success) and hierarchical composite endpoints (combined safety endpoint) were collected. Device success was achieved through 1) successful vascular access, successful delivery and deployment of the device, and successful retrieval of the delivery system; 2) correct positioning of the device in the proper anatomic location with the prosthetic heart valve performing as intended (aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, without moderate or severe paraprosthetic aortic regurgitation); and 3) the need to implant only one valve in the proper anatomic location. The combined safety endpoint was defined as a composite of all-cause death, major stroke, major vascular sequelae, life-threatening or disabling bleeding, acute kidney injury (stage 3), periprocedural myocardial infarction, and repeat surgical or interventional procedures for valve-related dysfunction. Structured follow-up involved the confirmation of vital status by contacting referring hospitals or each patient's family.

Statistical Analysis

Statistical analysis was performed with use of SPSS software version 17.0 (IBM Corporation; Somers, NY). Categorical variables were compared by means of the χ^2 or Fisher exact test and are presented as numbers and percentages. Normality of distribution for continuous variables, determined by means of the Shapiro-Wilk test, is presented as mean ± SD or as median and IQR. Continuous variables were compared by using the Student *t* or Wilcoxon rank sum test. The Wilcoxon signed rank test (for continuous variables) and the McNemar test conducted by exact methods (for binomial variables) were used to perform paired comparisons between pre-treatment and post-treatment echocardiographic results. A Kaplan-Meier survival curve was constructed. Two-sided *P* values <0.05 indicated statistical significance.

Results

Table I shows the baseline characteristics of the 53 patients who underwent TAVI. Their mean age was 79 ± 6 years, 40 were in NYHA class III or IV (75%), and 31 were men (58%). The predicted surgical risk was 25% according to logistic EuroSCORE and 6% according to the Society of Thoracic Surgeons score. Left ventricular ejection fraction was <0.35 in 9 of the patients (17%), and mean aortic valve area was 0.69 ± 0.19 cm^2 with a mean transvalvular gradient of 40 ± 17 mmHg. Aortic

TABLE I. Baseline Clinical and Echocardiographic Characteristics of the 53 Patients Who Underwent TAVI

Variable	Value
Age, yr	79 ± 6
Male sex	31 (58)
Height, cm	164 ± 8
Weight, kg	67 ± 10
Body mass index, kg/m^2	24.8 ± 3.5
Body surface area, m^2	1.75 ± 0.15
NYHA functional class III–IV	40 (75)
Previous myocardial infarction	2 (4)
Previous CABG	8 (15)
Previous PCI	11 (21)
Diabetes mellitus	14 (26)
Hypertension	50 (94)
Creatinine level, μmol/L	148 ± 220
Chronic hemodialysis	3 (6)
COPD	28 (53)
Permanent pacemaker	9 (17)
Atrial fibrillation	4 (8)
Logistic EuroSCORE, %	24.6 (17.4–34.4)
STS score, %	5.9 (3.2–8.3)
Left ventricular hypertrophy	
Mild	23 (43)
Moderate	17 (32)
Severe	2 (4)
Left ventricular dilation	
Mildly dilated	7 (13)
Dilated	11 (21)
LVEF ≤0.35	9 (17)
Aortic valve area, cm^2	0.69 ± 0.19
Aortic valve annulus, mm	20 ± 1.4
Peak velocity, m/s	4.23 ± 0.8
Transvalvular gradient, mmHg	40 ± 17
Aortic regurgitation	
Mild	28 (53)
Moderate	16 (30)
Severe	1 (2)
Mitral regurgitation	
Mild	30 (57)
Moderate	16 (30)
Severe	1 (2)

CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAVI = transcatheter aortic valve implantation

Data are presented as mean ± SD, median and interquartile range, or number and percentage.

regurgitation and mitral regurgitation were each moderate in 16 patients (30%) and severe in 1 patient (2%).

Thirty-Day Clinical Outcomes

Transcatheter aortic valve implantation was performed through the femoral artery in 50 patients, and through the left subclavian artery in 3 who had severe peripheral vascular disease. Table II summarizes the clinical outcomes. Five patients died. The 30-day mortality rate was 9% for all-cause death and 6% for cardiovascular death (3 patients). Of note, 4 of the 5 deaths occurred either during the original procedure (n=3) or during cardiac re-intervention (n=1). The intraprocedural deaths were due to coronary obstruction, retroperitoneal hemorrhage, and electromechanical complications, respectively. All deaths occurred in the earlier half of the cohort (March 2008 through November 2009). The technical composite endpoint (device success rate) was 77%. This is explained by paraprosthetic aortic regurgitation in 8 patients, valve-in-valve implantation in 2 patients, and failed vascular closure associated with fatal bleeding in 2 patients. The device success rate in the earlier half of the cohort was 74%, compared with 81% in the later half.

Cerebrovascular sequelae were diagnosed in 3 patients: major stroke in 2 (on day 1 and day 2, respectively) and a transient ischemic attack in one (on day 30). Vascular sequelae in 13 patients were associated with problematic functioning of the Prostar device in 10 patients, retroperitoneal hemorrhage in 2, and an access-site hematoma leading to a significant drop in hemoglobin in one. All these sequelae were associated with overt bleeding events. In total, there were 4 life-threatening or disabling, 7 major, and 4 minor overt bleeding events within the first 24 hours. Another 2 severe bleeding events occurred more than 24 hours after TAVI: one caused by cardiac tamponade, and one by a fatal retroperitoneal hemorrhage during re-intervention that involved balloon dilation of an underexpanded CoreValve prosthesis.

In 16 patients, a new permanent pacemaker was implanted because of 3rd-degree AV block (15 patients) and 2nd-degree AV block (1 patient). The indication for pacemaker implantation occurred during the procedure in 6 patients, after the procedure in 8, and after discharge from the hospital in 2 (day 10 and day 24).

The combined 30-day safety endpoint of 30% did not change between the 2 halves of the cohort.

Figure 1 shows the periprocedural echocardiographic results. CoreValve implantation resulted in a significant increase in aortic valve area from 0.7 ± 0.2 to 2.5 ± 0.6 cm^2 (P <0.001). This in turn reduced the peak transvalvular velocity from 4.2 ± 0.8 to 2 ± 0.5 m/s and the peak gradient from 74 ± 29 to 17 ± 8 mmHg (both P <0.001). After TAVI, fewer patients had moderate or severe mitral regurgitation (13% vs 32% at baseline, P=0.002).

TABLE II. Thirty-Day Cardiovascular and Noncardiovascular Sequelae, Prosthetic Valve-Associated Endpoints, and Therapy-Specific Endpoints in the 53 Patients Who Underwent TAVI*

Variable	No. (%)
Cardiovascular Complications	
30-day death	
All-cause	5 (9)**
Cardiovascular cause	3 (6)
Myocardial infarction	
Periprocedural	2 (4)
Spontaneous	0
Stroke	
Major	2 (4)
Minor	0
Transient ischemic attack	1 (2)
Vascular	
Major	12 (23)
Minor	1 (2)
Bleeding, <24 hr	
Life-threatening or disabling	4 (8)
Major	7 (13)
Minor	4 (8)
Bleeding, >24 hr	
Life-threatening or disabling	2 (4)
Major	0
Minor	0
Noncardiovascular Complications	
Acute kidney injury	
Stage 1	7 (13)
Stage 2	1 (2)
Stage 3	1 (2)
Combined safety endpoint (at 30 d)***	16 (30)
Prosthetic Valve-Associated Endpoints**	
New PPI	16 (30)
New PPI for 3rd-degree atrioventricular block	15 (28)
Therapy-Specific Endpoints	
Post-implantation balloon dilation	8 (15)
Valve-in-valve implantation	2 (4)
Unplanned cardiopulmonary bypass use	1 (2)
In-hospital re-intervention	1 (2)

PPI = permanent pacemaker implantation; TAVI = transcatheter aortic valve implantation

*Mutually nonexclusive analysis (≥1 event/patient possible) except for combined safety endpoint

**Includes 3 intraprocedural deaths

***Composite of all-cause death, major stroke, major vascular complication, life-threatening bleeding, acute stage 3 kidney injury, myocardial infarction, and repeat procedures for valve-related dysfunction

****There were no prosthetic valve-related occurrences of worsening mitral regurgitation or mitral valve stenosis, left ventricular outflow tract rupture, or new ventricular septal defect.

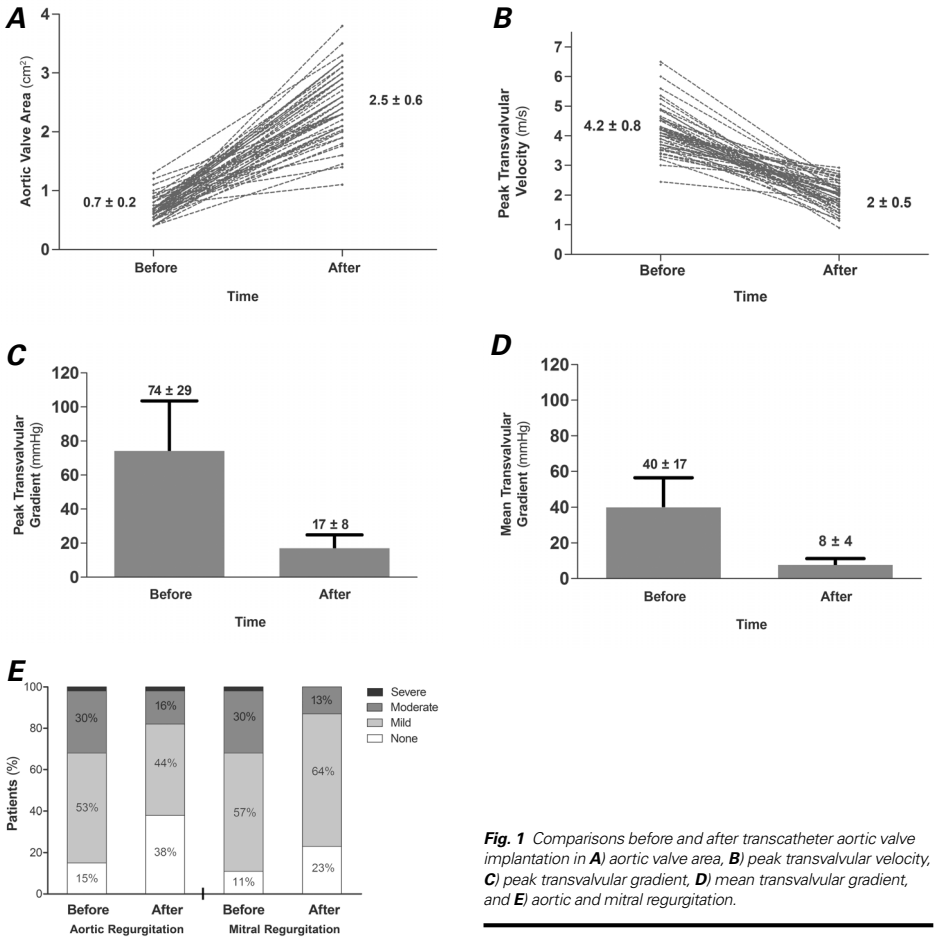


Fig. 1 *Comparisons before and after transcatheter aortic valve implantation in **A**) aortic valve area, **B**) peak transvalvular velocity, **C**) peak transvalvular gradient, **D**) mean transvalvular gradient, and **E**) aortic and mitral regurgitation.*

Clinical Follow-Up

Clinical follow-up was available for all patients and ranged from 0 to 16 months (median, 9 mo). During follow-up, 10 patients died at a median of 87 days after TAVI (IQR, 1–358 d). Of these, 5 died after discharge from the hospital at a median of 324 days after TAVI (IQR, 166–414 d). Three in-hospital deaths (60%) and 1 death after hospital discharge (20%) were cardiac-related. At 1 year, the survival rate was 81% (Fig. 2).

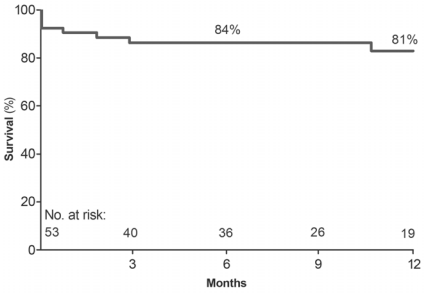


Fig. 2 *Kaplan-Meier survival curve after transcatheter aortic valve implantation.*

Discussion

In our early experience with CoreValve TAVI in a Latin American population, the short-term mortality rate was 9%—comparable to that in previous studies.[1,4,9-11] The

fact that most of our patients' deaths occurred during the procedure itself is most likely associated with a learning curve; our device success rates improved over time in parallel with lower mortality rates in the second half of the cohort.

Upon enrollment, our high-risk study population faced the poor prognosis associated with standard medical therapy alone. The patients presented with a median EuroSCORE of 25% and poor left ventricular function in 17% of cases. The 9% short-term mortality rate after TAVI (with a decrease to 4% in the second half of the cohort) seems to confirm the safety of this treatment in very high-risk patients. Nonetheless, 30% of the patients experienced a severe adverse event. The frequency of adverse events (the combined 30-day safety endpoint) did not decrease over time and was most often driven by problems at the access site during vascular closure. The importance of a learning curve has been described in previous studies, in which procedural success rates improved as a function of time and were subsequently associated with improved early survival rates.[12,13]

Vascular sequelae reportedly occur in 4% to 32% of patients and are associated with a 2- or 3-fold higher mortality rate.[14-16] In our study, all vascular sequelae were associated with a bleeding component (fatal in 2 patients) and were most often due to problematic functioning of the Prostar device. For these reasons, we currently prefer a more controlled and limited surgical cutdown to the femoral artery, with exposure of its surrounding tissues when peripheral calcification is present at the site of access. Also, the Prostar device was originally designed for puncture holes up to 10F in size.[17] Therefore, it seems reasonable to perform a limited surgical cutdown, because "off-label" application of the Prostar for the CoreValve requires the insertion of a large 18F sheath in the femoral artery.[18] If we are at all uncertain about hemostasis, we will routinely perform follow-up angiography to pinpoint contrast-medium leakage that might not be clinically visible at the end of the procedure. Given the importance of adequately preventing and managing vascular and bleeding sequelae during TAVI, it is prudent to visit institutions that have expertise in percutaneous femoral closure techniques before embarking upon a percutaneous transfemoral TAVI program.

In our study, a mean of 1.6 ± 2.3 units of red blood cells per patient were transfused, and 28 of the patients required 1 or more units while hospitalized; this is in accordance with previous reports.[19,20] Red blood cell transfusion is a predictor of acute kidney injury after TAVI, along with baseline renal dysfunction and contrast-medium administration during the procedure.[19-23] Stage 1, 2, or 3 acute kidney injury occurred in 17% of our patients, similar to findings of 12% to 28% in previous studies.[19-23] Measures to reduce the risk of acute kidney injury include strict application of a pre-hydration protocol preprocedurally when contrast-enhanced multislice computed tomography and left-sided heart catheterization are performed, and maintaining sufficient time between these imaging procedures and TAVI itself. Renal damage can be avoided by reducing contrast-medium administration and red blood cell transfusions, and by controlling hemodynamic status during and after the procedure. Finally, patients with acute kidney injury require close periprocedural monitoring of renal function and vital signs (heart rate, blood pressure, and urinary production), given their 2- to 3-fold higher risk of short- and long-term death.[19-21]

Although TAVI can be safe in very high-risk patients with AS, there may be an increased risk of perioperative stroke and encephalopathy during the immediate postprocedural period. The reported prevalence of stroke after TAVI ranges between 1% and 10%; however, the frequency of encephalopathy has rarely been documented.[10,24] Two of our patients had major ischemic strokes within 2 days postprocedurally, immediately after recovery from general anesthesia. Another patient had a transient ischemic attack on day 30, after hospital discharge. Encephalopathy, defined as delirium, coma, or seizures at any time during the postprocedural period, occurred in 4 patients (8%). Stroke and encephalopathy reportedly share similar pathophysiologic mechanisms, including microembolic formation or hypoperfusion induced by the procedure itself or occurring secondary to persistent atrial fibrillation. Well-established predictive factors after open-heart surgery include advanced age, hypertension, diabetes mellitus, and peripheral vascular disease[25]—all common comorbid conditions in our cohort. Existing patient-related predictive factors (such as septal wall thickness, noncoronary cusp thickness, and existing right bundle branch block) can be distinguished from procedure-related factors (including depth of valve implantation within the left ventricular outflow tract, prosthesis expansion after implantation, and type of prosthesis).

Conduction abnormalities frequently occur during TAVI, and with use of the CoreValve in particular. After CoreValve implantation, the prevalence of new left bundle branch block has ranged from 29% to 65%, 3rd-degree AV block from 15% to 44%, and permanent pacemaker implantation from 9% to 49%.[4,26-29] In comparison, after implantation of the SAPIEN valve (Edwards Lifesciences LLC; Irvine, Calif), the corresponding ranges in prevalence have been 6% to 18%, 0 to 27%, and 0 to 27%.[1,30-32] A new permanent pacemaker was implanted in 16 of our patients (30%) during hospitalization or within 30 days after TAVI. The new conduction abnormality for which a new permanent pacemaker was implanted occurred during TAVI in 6 of these patients and after TAVI in the others. In view of the large number of patients who developed 3rd-degree AV block after the procedure, we have sub-

stantially lowered our threshold for implanting a pacemaker.

From a technical standpoint, TAVI significantly increased aortic valve area and reduced the transvalvular gradient. The subsequent reduction in afterload may explain our observed reduction in severe mitral regurgitation, from 32% at baseline to 13% after TAVI. These findings suggest that coexisting severe mitral regurgitation—currently a contraindication for CoreValve implantation, according to the manufacturer's guidelines—might not always preclude TAVI in high-risk AS patients. Dedicated prospective echocardiographic studies are warranted to determine which patients with combined AS and severe mitral regurgitation might benefit from TAVI.

In our study, actuarial survival at 1 year was 81% (10 deaths), similar to that in the most recent registries.[1,10,33] Five of the deaths can be attributed to the procedure itself, whereas the other 5 patients died approximately 1 year after TAVI and predominantly of noncardiovascular causes. This suggests that short-term survivors of TAVI have a more favorable prognosis than do patients remaining on medical therapy, with its annual mortality rates of 25%. We are disappointed that many of our patients could not be offered TAVI, chiefly because of limited patient accessibility to the treatment. In addition, aortic balloon valvuloplasty does not seem to meet the clinical needs of high-risk AS patients. In our patients, the mortality rate after balloon valvuloplasty was 50%.

Limitations

The data used for this study were prospectively collected, but the analyses were performed on a relatively small sample of 53 patients. Therefore, this study does not permit firm conclusions, despite the fact that the direction of outcomes is in accordance with those of previous reports.

Conclusion

Transcatheter aortic valve implantation with the Medtronic CoreValve System in this Latin American population was associated with promising results, as evidenced by a short-term mortality rate of 9% and sustained 1-year results. Nevertheless, 30% of the patients experienced a severe adverse event, which is most likely explained by the nature of TAVI, the baseline risk of the patients under treatment, and the learning curve of the medical personnel.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597-607.
2. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106(24):3006-8.
3. Grube E, Schuler G, Buellesfeld L, Gerckens U, Linke A, Wenaweser P, et al. Percutaneous aortic valve replacement for severe aortic stenosis in high-risk patients using the second- and current third-generation self-expanding CoreValve prosthesis: device success and 30-day clinical outcome. J Am Coll Cardiol 2007;50(1):69-76.
4. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, et al. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4(2):242-9.
5. Buellesfeld L, Wenaweser P, Gerckens U, Mueller R, Sauren B, Latsios G, et al. Transcatheter aortic valve implantation: predictors of procedural success--the Siegburg-Bern experience. Eur Heart J 2010;31(8):984-91.
6. de Jaegere P, van Dijk LC, Laborde JC, Sianos G, Orellana Ramos FJ, Lighart J, et al. True percutaneous implantation of the CoreValve aortic valve prosthesis by the combined use of ultrasound guided vascular access, Prostar(R) XL and the TandemHeart(R). EuroIntervention 2007;2(4):500-5.
7. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57(3):253-69.
8. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2(5):358-67.
9. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32(2):198-204.
10. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123(3):299-308.
11. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, et al. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J 2011;32(2):191-7.
12. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation 2007;116(7):755-63.
13. Nuis RJ, van Mieghem NM, van der Boon RM, van Geuns RJ, Schultz CJ, Oei FB, et al. Effect of experience on results of transcatheter aortic valve implantation using a Medtronic CoreValve System. Am J Cardiol 2011;107(12):1824-9.
14. Van Mieghem NM, Nuis RJ, Piazza N, Apostolos T, Ligthart J, Schultz C, et al. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. EuroIntervention 2010;5(6):673-9.
15. Tchetche D, Dumonteil N, Sauguet A, Descoutures F, Luz A, Garcia O, et al. Thirty-day outcome and vascular complications after transarterial aortic valve implantation using both Edwards Sapien and Medtronic CoreValve bioprostheses in a mixed population. EuroIntervention 2010;5(6):659-65.

16. Kahlert P, Al-Rashid F, Weber M, Wendt D, Heine T, Kottenberg E, et al. Vascular access site complications after percutaneous transfemoral aortic valve implantation. Herz 2009;34(5):398-408.
17. Baim DS, Knopf WD, Hinohara T, Schwarten DE, Schatz RA, Pinkerton CA, et al. Suture-mediated closure of the femoral access site after cardiac catheterization: results of the suture to ambulate and discharge (STAND I and STAND II) trials. Am J Cardiol 2000;85(7):864-9.
18. Morasch MD, Kibbe MR, Evans ME, Meadows WS, Eskandari MK, Matsumura JS, Pearce WH. Percutaneous repair of abdominal aortic aneurysm. J Vasc Surg 2004;40(1):12-6.
19. Nuis RJ, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, et al. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2011;77(6):881-9.
20. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochelliere R, Doyle D, et al. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2010;31(7):865-74.
21. Sinning JM, Ghanem A, Steinhauser H, Adenauer V, Hammerstingl C, Nickenig G, Werner N. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010;3(11):1141-9.
22. Aregger F, Wenaweser P, Hellige GJ, Kadner A, Carrel T, Windecker S, Frey FJ. Risk of acute kidney injury in patients with severe aortic valve stenosis undergoing transcatheter valve replacement. Nephrol Dial Transplant 2009;24(7):2175-9.
23. Van Linden A, Kempfert J, Rastan AJ, Holzhey D, Blumenstein J, Schuler G, et al. Risk of acute kidney injury after minimally invasive transapical aortic valve implantation in 270 patients. Eur J Cardiothorac Surg 2011;39(6):835-43.
24. Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, et al. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv 2008;1(3):167-75.
25. McKhann GM, Grega MA, Borowicz LM Jr, Baumgartner WA, Selnes OA. Stroke and encephalopathy after cardiac surgery: an update. Stroke 2006;37(2):562-71.
26. Baan J Jr, Yong ZY, Koch KT, Henriques JP, Bouma BJ, Vis MM, et al. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. Am Heart J 2010;159(3):497-503.
27. Roten L, Wenaweser P, Delacretaz E, Hellige G, Stortecky S, Tanner H, et al. Incidence and predictors of atrioventricular conduction impairment after transcatheter aortic valve implantation. Am J Cardiol 2010;106(10):1473-80.
28. Erkapic D, Kim WK, Weber M, Mollmann H, Berkowitsch A, Zaltsberg S, et al. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. Europace 2010;12(8):1188-90.
29. Piazza N, Nuis RJ, Tzikas A, Otten A, Onuma Y, Garcia-Garcia H, et al. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. EuroIntervention 2010;6(4):475-84.
30. Sinhal A, Altwegg L, Pasupati S, Humphries KH, Allard M, Martin P, et al. Atrioventricular block after transcatheter balloon expandable aortic valve implantation. JACC Cardiovasc Interv 2008;1(3):305-9.
31. Gutierrez M, Rodes-Cabau J, Bagur R, Doyle D, DeLarochelliere R, Bergeron S, et al. Electrocardiographic changes and clinical outcomes after transapical aortic valve implantation. Am Heart J 2009;158(2):302-8.
32. Thielmann M, Wendt D, Eggebrecht H, Kahlert P, Massoudy P, Kamler M, et al. Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. Ann Thorac Surg 2009;88(5):1468-74.
33. Lefevre T, Kappetein AP, Wolner E, Nataf P, Thomas M, Schachinger V, et al. One year follow-up of the multi-centre European PARTNER transcatheter heart valve study. Eur Heart J 2011;32(2):148-57.

CHAPTER 13.2

Valve-in-Valve-in-Valve TAVI for the treatment of a degenerated surgical bioprosthesis in sub-aortic position

Case Reports

Valve-in-Valve-in-Valve Transcatheter Aortic Valve Implantation

to Treat a Degenerated Surgical Bioprosthesis in a Subaortic Position

Rutger-Jan Nuis, MD, PhD
Luis M. Benitez, MD
Carlos A. Nader, MD
Sergio Perez, MD
Eduardo J. de Marchena, MD
Antonio E. Dager, MD

Transcatheter aortic valve implantation for aortic stenosis has evolved as an alternative treatment for patients who are at high or excessive surgical risk. We report the case of an 84-year-old man with a degenerated surgically implanted valve in a subaortic position (9 mm below the native annulus) who underwent "valve-in-valve" transcatheter aortic valve implantation with use of a Medtronic CoreValve system. We planned to deploy the CoreValve at a conventional depth in the left ventricular outflow tract; we realized that this might result in paravalvular regurgitation, but it would also afford a "deep" landing site for a second valve, if necessary. Ultimately, we implanted a second CoreValve deep in the left ventricular outflow tract to seal a paravalvular leak. The frame of the first valve—positioned at the conventional depth—enabled secure anchoring of the second valve in a deeper position, which in turn effected successful treatment of the failing subaortic surgical prosthesis without paravalvular regurgitation. ***(Tex Heart Inst J 2013;40(3):323-9)***

Key words: *Aortic valve insufficiency/surgery; bioprosthesis; heart valve prosthesis implantation/instrumentation/methods; intention-to-treat analysis; reoperation/methods; risk assessment; treatment outcome*

From: *Erasmus ThoraxCenter (Dr. Nuis), 3015 CE, Rotterdam, The Netherlands; Angiografia de Occidente S.A. (Drs. Benitez, Dager, Nader, and Perez), Cali, Colombia; and Department of Medicine (Dr. de Marchena), Miller School of Medicine, University of Miami, Miami, Florida 33136*

Dr. Nuis received an Erasmus-Columbus Grant (www.erasmus-columbus.eu) in support of this work.

Address for reprints: *Rutger-Jan Nuis, MD, PhD, Erasmus ThoraxCenter, 's-Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands*

E-mail: *r.nuis@erasmusmc.nl*

Transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement for the treatment of aortic stenosis in patients who are at high or excessive operative risk.[1] It has been shown that implanting a transcatheter valve within a failing surgical valve ("valve-in-valve") is safe and effective.[2] However, the feasibility of this intervention for failing valves in subaortic position has not been reported. The implantation of a self-expandable transcatheter valve at a deep level in the left ventricular outflow tract (LVOT) (with inflow portion >8 mm below the noncoronary cusp) could expectedly be associated with an increased risk of paravalvular regurgitation, valve dislodgment, or both, because of insecure anchoring of the prosthesis in the lower anatomic structures of the LVOT.[3] We report the case of a patient in whom we implanted 2 CoreValve® devices (Medtronic, Inc.; Minneapolis, Minn), to safely replace a failing surgical bioprosthesis in a subaortic position.

Case Report

In December 2011, an 84-year-old man presented with increasing dyspnea, New York Heart Association (NYHA) functional class III, and a history of congestive heart failure, coronary artery disease, and aortic stenosis. At the age of 74 years, he had undergone coronary artery bypass grafting that had involved a left internal mammary artery anastomosis to the left anterior descending coronary artery and saphenous vein grafts to the right coronary artery and obtuse marginal branch. Concomitantly, surgical aortic valve replacement was performed with implantation of a 21-mm stentless bioprosthesis (Labcor Laboratorios Ltda.; Belo Horizonte, Brazil). Postoperatively, the patient developed symptoms associated with patient–prosthesis mismatch and a mean transvalvular gradient of 40 mmHg. Therapy with β-blockers yielded symptom-free survival for 10 years, whereupon sudden deterioration occurred and the patient presented with heart-failure symptoms. Echocardiography showed a left ventricular (LV) ejection fraction of 0.55 with mild LV dilation, a mean transvalvular gradient of 15 mmHg, an LV pseudoaneurysm, and a failing, subaortic-positioned bioprosthesis that was causing severe central and paravalvular regurgitation.

Screening for valve-in-valve TAVI was performed. Multislice computed tomography (MSCT) and cardiac and peripheral angiography showed patent grafts, grade 3

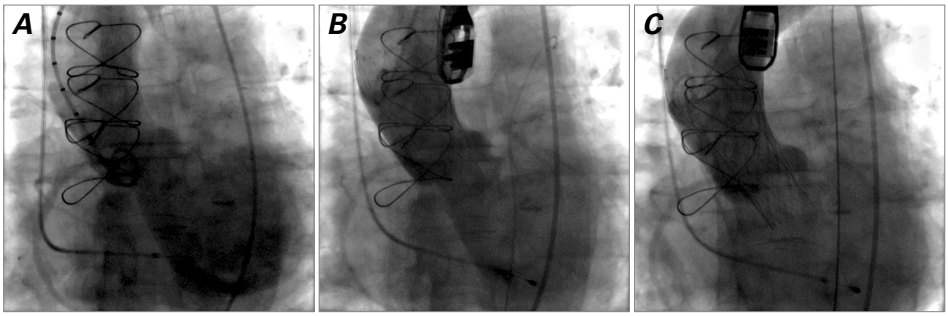


Fig. 1 *Fluoroscopy **A**) shows severe aortic regurgitation before implantation of the first valve; **B**) after implantation, the inflow portion of the valve is 4 mm from the noncoronary cusp. Despite complete expansion of the CoreValve frame, grade 3 aortic regurgitation persisted. **C**) After implantation of the second CoreValve, the inflow portion is 13 mm from the noncoronary cusp, and no aortic regurgitation is observed.*

aortic regurgitation, and a peripheral vascular tree of more than 7 mm in luminal diameter. In view of the patient's age and the high risk of repeat open surgery, it was decided to perform transfemoral TAVI with use of a 26-mm CoreValve. However, MSCT revealed that the surgically implanted bioprosthesis was in a subaortic position, approximately 9 mm below the native annulus. This prompted debate regarding how deeply the CoreValve should be implanted within the LVOT to achieve successful bioprosthetic replacement without valve dislodgment, paravalvular regurgitation, or both, because of insecure anchoring of the CoreValve so deeply in the LVOT.[2]

We planned to insert a second CoreValve if the first—positioned conventionally with its inflow portion 6 to 8 mm from the noncoronary cusp—failed to control the paravalvular leak. If leakage persisted, it was thought that the frame of the first valve would facilitate secure anchoring of the second valve deeper in the LVOT, thereby replacing the failing subaortic bioprosthesis with minimal risk of valve dislodgment.

The patient was given local anesthesia with mild sedation. The procedure was performed with use of cine and fluoroscopic guidance and monitoring with transesophageal echocardiography (TEE). After the failing bioprosthesis was crossed with a straight wire that was exchanged for a stiff support wire, the CoreValve delivery catheter was positioned in the LVOT with the ventricular edge 10 mm from the noncoronary cusp. However, the final valve landing was only 4 mm from the cusp, because of upward migration during frame expansion of the CoreValve. Immediately thereafter, hemodynamic tracings and fluoroscopy showed severe aortic regurgitation and a blood pressure of 160/40 mmHg (Fig. 1).

According to TEE, the CoreValve was 4 mm from the noncoronary cusp. The failing bioprosthesis remained visible, with active leaflet movement just below the CoreValve (Fig. 2). At this stage, preparations were made to implant the second valve deep within the LVOT, to safely replace the failing, subaortic-positioned surgical valve.

The second CoreValve was positioned with its inflow portion 9 mm lower than that of the first CoreValve, 13 mm below the noncoronary cusp and 4 mm superior to the hinge point of the anterior mitral leaflet. Aortography and fluoroscopy revealed an excellent technical result, without aortic regurgitation (Fig. 1C) or mitral dysfunction, and with improved hemodynamics: the patient's blood pressure was 140/70 mmHg. Follow-up MSCT confirmed that the second CoreValve had covered both the bioprosthesis and the first CoreValve (Fig. 3). The patient was discharged from the hospital after 4 days, asymptomatic and in NYHA functional class I; he remained in that functional class as of May 2013.

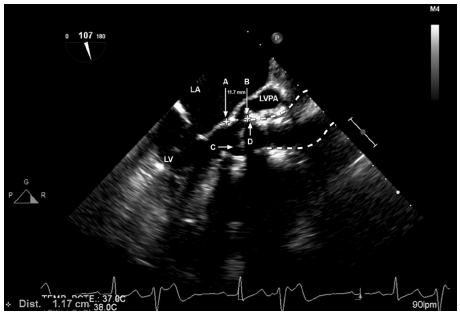


Fig. 2 *Transesophageal echocardiogram shows the first CoreValve with the inflow portion 4 mm below the native annulus, and the failing bioprosthesis just inferior to the CoreValve.*

A = hinge point of anterior mitral leaflet; B = ring of degenerated bioprosthesis; C = leaflet of degenerated bioprosthesis; D = inflow portion of the CoreValve; LA = left atrium; LV = left ventricle; LVPA = left ventricular pseudoaneurysm

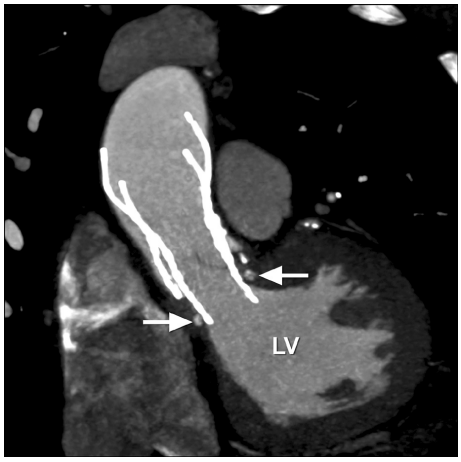


Fig. 3 *Multislice computed tomogram (sagittal view) shows the second CoreValve positioned within the first CoreValve and the degenerated bioprosthesis. Arrows indicate the ring of the failing surgical bioprosthesis.*

Discussion

Consequent to greater use of TAVI in clinical practice, interest has increased in treating degenerated surgical bioprostheses with valve-in-valve procedures.[2] The subaortic position of the failing bioprosthesis in our patient necessitated an exceptionally deep CoreValve landing in the LVOT—13 mm below the noncoronary cusp—instead of the usual 6 to 8 mm for which the device is designed. Such a deep landing increases the risk of paravalvular leak, valve dislodgment, or both, because of insecure anchoring of the prosthesis in the deep anatomic structures of the LVOT.[2,3] Accordingly, we chose to implant 2 CoreValve devices, with one of them positioned deeply and anchored securely in the LVOT. The second successfully replaced the failing subaortic bioprosthesis (Fig. 3).

An important factor associated with this deep implant location relates to mitral valve function: the ventricular end of the valve-support frame might interfere with the mobility of the anterior mitral leaflet and alter the geometry of the mitral annulus, leading to (new) mitral valve dysfunction. De Chiara and colleagues[4] showed that the implantation depth of a CoreValve prosthesis was an independent predictor of worsening mitral regurgitation. In our case, the distance between the failing bioprosthesis and the hinge point of the anterior mitral leaflet was 11.7 mm, which enabled deep positioning of the CoreValve in the LVOT without causing new mitral dysfunction (Fig. 2).

Similar to low implant locations, a "high" implantation can also occur as a result of valve dislocation from insecure anchoring during or immediately after valve positioning. This could lead to coronary artery obstruction because of impingement of the coronary ostia by the valve-support structure. Although this sequela is encountered in less than 1% of cases, it frequently necessitates emergency revascularization by means of percutaneous coronary intervention or open-heart surgery.[5]

For these reasons, correct positioning of the bioprosthesis in the aortic annulus is crucial during TAVI. Although the ideal location of the inflow portion of the CoreValve is 6 to 8 mm from the noncoronary cusp, our patient's case shows that a very low implant location might be necessary in patients who present with a degenerated valve in a subaortic position. Careful preprocedural planning (in deciding upon the use of 1 or 2 CoreValve devices) and a pre- and periprocedural team approach between cardiologists and imaging specialists (in deciding upon the correct implant location) can enable safe TAVI in a patient with a failing subaortic bioprosthesis.

References

1. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364(23):2187-98.
2. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 1). JACC Cardiovasc Interv 2011;4(7):721-32.
3. Van Mieghem NM, Schultz CJ, van der Boon RM, Nuis RJ, Tzikas A, Geleijnse ML, et al. Incidence, timing, and predictors of valve dislodgment during TAVI with the Medtronic CoreValve System. Catheter Cardiovasc Interv 2012;79(5):726-32.
4. De Chiara B, Moreo A, De Marco F, Musca F, Oreglia J, Lobiati E, et al. Influence of CoreValve ReValving System implantation on mitral valve function: an echocardiographic study in selected patients. Catheter Cardiovasc Interv 2011;78(4):638-44.
5. Stabile E, Sorropago G, Cioppa A, Cota L, Agrusta M, Lucchetti V, Rubino P. Acute left main obstructions following TAVI. EuroIntervention 2010;6(1);100-5.

PART 7

DISCUSSION

Summary and discussion

SUMMARY AND GENERAL DISCUSSION

Transcatheter aortic valve implantation (TAVI) is increasingly used to treat patients with aortic stenosis who are considered at high or excessive risk for surgical valve replacement (AVR)[1-4]. The aim of this thesis was to provide insights into the potential current and future role of TAVI in the treatment of patients with aortic stenosis who are at high (currently) and eventually lower risk (future) for AVR by addressing the frequency, pathophysiology and prognostic effects of various complications that are characteristic to TAVI.

Part I. Clinical decision-making, complications and effect of experience

In Chapter 2, we found that approximately two thirds of the patients who are referred for TAVI receive TAVI, 7% undergoes AVR and 28% receives medical treatment (i.e. no valve replacement). Reasons to decline TAVI in favour of AVR or medical therapy include patient's preference (29%), peripheral vascular disease (15%) and non-severe aortic stenosis (11%). Although direct comparisons cannot be made due to the absence of randomized treatment allocation, mortality is lower after TAVI compared to medical treatment at 6 months, 1 year and 2 years. These data, nevertheless, confirm the dismal prognosis in patients with aortic stenosis who are referred for further treatment but do not undergo valve replacement or implantation.

Chapter 3 provides an overview of the complications that occur during and after TAVI. TAVI is associated with ≥1 cardiovascular and/or non-cardiovascular event in 51% of the patients; permanent pacemaker implantation is needed in another 8%, and TAVI is truly uncomplicated in 41%. Patients who suffer a complication or undergo additional pacemaker implantation have a hospital stay of 14 days which is 2 times longer than patients who have an uncomplicated peri-operative course.

Because TAVI concerns a new treatment for patients at high or even extreme risk for AVR, outcome after TAVI particularly depends on the patient baseline risk profile, operator experience, and progress in technology and technique. In Chapter 4, we compared the results of TAVI during the initiation phase and after certification to perform TAVI with the Medtronic CoreValve System without the presence of a proctor. The increasing familiarity with the procedure allowed the proposals of simplification of the procedure that were subsequently applied in practice, which transformed the complexity of the procedure gradually with a better outcome albeit that there was still a significant number of peri-operative (major cardiovascular) complications.

Part II. Frequency, pathophysiology and persistence of new conduction abnormalities

New-onset left bundle branch block and complete atrioventricular block frequently occur during and after TAVI and often lead to the implantation of a permanent pacemaker[5]. These conduction abnormalities (CAs) are more common following the implantation of the self-expandable Medtronic CoreValve as compared to the balloon-expandable Edwards

Sapien valve implantation (up to 65 and 27%, respectively)[6, 7]. In Chapter 5, we used continuous 12-lead ECG analyses during TAVI and found that >80% of the patients developed a new CA during or after CoreValve implantation and that 75% of these CAs persisted until hospital discharge. We also found that more than half of these CAs occurred during balloon pre-dilation (i.e. before the actual valve implantation) and that patients who developed a new CA during balloon valvuloplasty had a significantly higher balloon/annulus ratio than those who did not. Given the preponderance of new CAs during balloon valvuloplasty and its relationship with the balloon/annulus ratio, the findings indicate that new CAs (and potentially new PPI) can substantially be reduced by using a balloon/annulus ratio close to 1.0. We also found that new CAs following the implantation of the Medtronic CoreValve System persist until 6 months after TAVI.

PART III. Frequency and pathophysiology of cerebrovascular complications

We found that stroke/TIA occurred in 9% of the patients and that more than half of these events occurred >24 hours after the procedure. Brain computed tomography showed a cortical infarct in most patients (42%) and a lacunar infarct in 26%. New-onset atrial fibrillation was associated with a 4-fold higher risk of stroke and all patients who suffered a stroke beyond 24 hours after TAVI also had (an episode of) new atrial fibrillation after TAVI. Of note none of these patients had received anticoagulant therapy at the time of the event. In line with these findings, we found in a multicenter study that stroke occurred in 5.1% of the patients of which approximately half of the events occurred >24 hours after the procedure (Chapter 9). Determinants of stroke that occurs within 24 hours were balloon dilation of the valve immediately after implantation and valve dislodgment or embolization. New-onset atrial fibrillation was found to be associated with stroke that occurs after 24 hours following the procedure. Stroke occurring after hospital discharge is seen in another 3.3% of the patients and is associated with pre-existent chronic atrial fibrillation, peripheral vascular disease and prior cerebrovascular disease. In addition to the devastating effects on quality of life, stroke was also found to be an independent predictor of both 30-day and late-mortality.

The fact that approximately half of the strokes occur after TAVI, which are in turn associated with the development of postoperative new onset atrial fibrillation indicates that - in a number of patients - there is no direct relationship between the intervention itself and the development of a stroke, and that clinical rather than technical or procedural factors play a more important role in the occurrence of perioperative stroke. It is, therefore, conceivable that preventive measures should above all be directed at improved postoperative management and, that endovascular embolic protection devices used during the procedure – as increasingly advocated – may reduce stroke only in a certain proportion of patients if proven to be safe and effective[8]. This is further supported by the fact that 26% of the strokes were lacunar, which is widely regarded as caused by cerebral hypo-perfusion in the presence of local atherosclerosis. This also suggests that all efforts should be made during TAVI to maintain adequate blood pressure and, thus, brain perfusion.

PART IV. Frequency and pathophysiology of acute kidney injury

In Chapter 10, we found that acute kidney injury (AKI) occurred in 19% of the patients following TAVI of whom 2% needed temporary hemodialysis. Blood transfusion was found to be an independent predictor of AKI, which in turn was independently associated with both 30-day and 1-year mortality. In Chapter 11, we sought to elucidate in more detail the relation between blood transfusion and AKI in addition to the effects on short- and long-term mortality in a much larger cohort of patients. We found AKI to occur in 21% of the patients. The number of units of blood transfusion ≤24 hr was the strongest predictor of AKI. Factors that may trigger the administration of transfusion such as baseline anemia, bleeding-vascular complications and peri-operative blood loss were not found to predict AKI. Also, it was found that patients with severe baseline anemia had 2.4 times less blood loss but received 2.3 fold more units of blood in comparison to patients without anemia before TAVI. This suggests either an unconscious or better control of hemostasis during TAVI in patients with severe baseline anemia and/or a lower threshold for administering transfusion during TAVI in such patients. With respect to the prognostic effects, AKI and life-threatening bleeding were independent predictors of 30-day mortality (OR: 3.04 [1.52-6.07], OR: 5.39 [2.14-13.57], respectively) while blood transfusion (≥3 units), baseline anaemia and AKI predicted mortality beyond 30 days. The clinical translation is that outcome of TAVI may be improved by a more restrictive use of transfusions that should be directed by more strict guidelines for blood transfusion therapy.

PART V. Effects of pre-operative anemia and blood transfusions

In Chapter 12, we found that the prevalence of pre-operative anemia in patients undergoing TAVI was 57%, which is higher than reported in elderly patients undergoing cardiac (surgical) interventions (up to 36%). Independent determinants of pre-operative anemia were - in descending order of odds - pre-operative mitral regurgitation grade ≥III, history of heart failure, diabetes, male gender, peripheral vascular disease and body mass index. Although anemia as a binary variable was a weak independent determinant of 30-day mortality, the severity of anemia (preoperative Hb level) was the strongest predictor of mortality at 1 year with a hazard ratio of 2.92 (95% CI: 1.66-5.13) in patients with Hb <10 g/dl. Moreover, patients with anemia received 2 times more often ≥1 blood transfusion in comparison to patients without anemia and, more importantly, blood transfusion independently predicted mortality at 30 days and during follow-up. It remains to be elucidated whether the correction of anemia and/or its treatment will beneficially affect outcome but the data of the present study indicate that blood transfusion therapy should be used cautiously.

FUTURE CHALLENGES

The clinical application of catheter-based aortic valve implantation via a peripheral blood vessel was first performed by Alain Cribier et al in 2002 in France[9]. It is the result of an intrinsic feature of mankind, namely the drive to innovate and of a remarkably short but intense period of iteration and structural and functional testing of frames and leaflets in the preclinical setting that has lead to the development of a prosthesis suitable for use in clinical practice.

Hard to grasp how such a concept would prove to be applicable and beneficial for patients, it was embraced by some and received with suspicion by others. Nevertheless, the shear increase in the number of procedures and institutions performing this procedure by itself preceding the results of randomized comparisons (TAVI vs. AVR) simply forecasts its future. At the time of this writing (March 2013), it is estimated that approximately 75.000 patients have undergone TAVI in 500 centers around the world. The number of patients treated so far contrasts with the number of patients enrolled in 2 pivotal randomized studies (PARTNER A & B, in total 1057 patients) of which the data have been published in a pear reviewed medical journal[1-4]. Therefore, it is fair to conclude that TAVI will enjoy the same fate as percutaneous coronary intervention as predicted by M. Mack[10].

The data of the PARTNER studies have shown that selected patients who receive TAVI indeed benefit from the procedure in terms of survival and quality of life[1-4]. Of note, these studies used a prosthesis that by current standards may be considered obsolete given the large size of the delivery catheters used in these studies. With the clinical use of smaller catheters and forecasted advent of even smaller ones, it is not difficult to foresee its future in terms of application and expansion.

Yet, TAVI remains an invasive procedure used in patients with degenerative calcified aortic stenosis. It is, thus, not surprising that TAVI is invariably associated with substantial risks that are of a more general (i.e. seen in invasive procedures) and more specific to TAVI. The data of this thesis indicate that the underlying risk is multi-factorial. As shown, distinction can be made between patient-, procedure/physician/institution-, and device-related factors explaining the occurrence of complications. It should, however, be noted that while we have shown that these factors may predict the occurrence of a complication, the statistical method used (i.e. multivariable analysis) does not allow to draw conclusions on the nature of the association (e.g. causal).

Irrespective of the nature of the association between a variable and outcome found in this thesis, it is clear that outcome will improve by further reducing the size of the delivery catheter[11]. While at the beginning of TAVI delivery catheters of 24/25 Fr (transfemoral) and 33 Fr (transapical) were used, they are currently 16 and 24 Fr, respectively[12]. Catheters of 14e Fr will be soon available. The down-sizing of these catheters will further reduce bleeding- and vascular complications as a result of which one may expect a further decrease of mortality and also complications such as acute kidney injury.

The devastating complication of stroke may be reduced by improved postoperative care (e.g. by a more strict and adequate response in case a patient develops new onset atrial fibrillation) and, eventually the use of filters placed in the cerebral arteries that capture

embolic debris that is liberated during the procedure. It remains, however, to be seen whether the use of such a filters will reduce stroke. For that purpose, a randomized study has been initiated and started in Rotterdam (CLARET).

Conduction abnormalities may be reduced by improved control of the release of the prosthesis. Experience with TAVI plays a minor role as demonstrated in this thesis, but improved ergonomics of the delivery catheter and of technique of release (e.g. motorized) is expected to help. The question is whether novel software that helps the physician to continuously define the base of the aortic root during the procedure will improve the correctness of positioning. Perhaps, all factors combined will ultimately prove to be beneficial with an added value of each individual component of improvement. Yet, most of the improvement is to be expected from advancements in the design and function of the frame of the bioprosthesis. At present a lot of effort is invested into the possibility to fully retrieve the valve in case of an inadequate position. One such valves (i.e. Portico, St Jude, Minneapolis, USA) has already entered the clinical arena and has received CE approval[13].

The same holds for addressing paravalvar aortic regurgitation[14]. In addition to the correctness of positioning, an extra skirt at the inflow region of the prosthesis has been added to the balloon expandable bioprosthesis (Edwards Life Sciences). Such a change in design may proof to be essential since – at variance with AVR – the calcium is not removed during TAVI. This calcium may prevent complete or adequate frame expansion leading to paravalvar aortic regurgitation[15, 16]. Also, the use and understanding of 3-dimensional imaging will help to improve outcome by improved patient planning and evaluation[17, 18].

The cycle of iterations in design, increase in clinical experience and ongoing clinical research assessing the role of TAVI relative to AVR but also, and perhaps in particular, observational cohort research in large series of patients who are more close to most patients seen in clinical practice will lead to ongoing improvements in outcome. This cycle also allows new proposals of improvement in terms of patient selection, procedure planning and execution and, postoperative care in addition to insights how to improve the next generation of prostheses. Critical assessment in accordance with clinical scientific and ethical principals will boost the future of TAVI to the benefit of care of patients with valvular heart disease. It will not be restricted to the aortic valve.

References

1. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363:1597-1607.

2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson

WN, Wang D, Pocock SJ, Investigators PT. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364:2187-2198.

3. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR, Leon MB, Investigators PT. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. *N Engl J Med.* 2012;366:1696-1704.

4. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB, Investigators PT. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med.* 2012;366:1686-1695.

5. van der Boon RM, Nuis RJ, Van Mieghem NM, Jordaens L, Rodes-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PP. New conduction abnormalities after TAVI--frequency and causes. *Nat Rev Cardiol.* 2012;9:454-463.

6. Baan J, Jr., Yong ZY, Koch KT, Henriques JP, Bouma BJ, Vis MM, Cocchieri R, Piek JJ, de Mol BA. Factors associated with cardiac conduction disorders and permanent pacemaker implantation after percutaneous aortic valve implantation with the CoreValve prosthesis. *Am Heart J.* 2010;159:497-503.

7. Thielmann M, Wendt D, Eggebrecht H, Kahlert P, Massoudy P, Kamler M, Erbel R, Jakob H, Sack S. Transcatheter aortic valve implantation in patients with very high risk for conventional aortic valve replacement. *Ann Thorac Surg.* 2009;88:1468-1474.

8. Nietlispach F, Wijesinghe N, Gurvitch R, Tay E, Carpenter JP, Burns C, Wood DA, Webb JG. An embolic deflection device for aortic valve interventions. *JACC Cardiovasc Interv.* 2010;3:1133-1138.

9. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation.* 2002;106:3006-3008.

10. Mack M. Fool me once, shame on you; fool me twice, shame on me! A perspective on the emerging world of percutaneous heart valve therapy. *J Thorac Cardiovasc Surg.* 2008;136:816-819.

11. Van Mieghem NM, Nuis RJ, Piazza N, Apostolos T, Ligthart J, Schultz C, de Jaegere PP, Serruys PW. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. *EuroIntervention.* 2010;5:673-679.

12. Walther T, Simon P, Dewey T, Wimmer-Greinecker G, Falk V, Kasimir MT, Doss M, Borger MA, Schuler G, Glogar D, Fehske W, Wolner E, Mohr FW, Mack M. Transapical minimally invasive aortic valve implantation: multicenter experience. *Circulation.* 2007;116:I240-245.

13. Willson AB, Rodes-Cabau J, Wood DA, Leipsic J, Cheung A, Toggweiler S, Binder RK, Freeman M, DeLarochelliere R, Moss R, Nombela-Franco L, Dumont E,

Szummer K, Fontana GP, Makkar R, Webb JG. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. *J Am Coll Cardiol.* 2012;60:581-586.

14. Genereux P, Head SJ, Hahn R, Daneault B, Kodali S, Williams MR, van Mieghem NM, Alu MC, Serruys PW, Kappetein AP, Leon MB. Paravalvular Leak After Transcatheter Aortic Valve Replacement: The New Achilles' Heel? A Comprehensive Review of the Literature. *J Am Coll Cardiol.* 2013.

15. Gripari P, Ewe SH, Fusini L, Muratori M, Ng AC, Cefalu C, Delgado V, Schalij MJ, Bax JJ, Marsan NA, Tamborini G, Pepi M. Intraoperative 2D and 3D transoesophageal echocardiographic predictors of aortic regurgitation after transcatheter aortic valve implantation. *Heart.* 2012;98:1229-1236.

16. Abdel-Wahab M, Zahn R, Horack M, Gerckens U, Schuler G, Sievert H, Eggebrecht H, Senges J, Richardt G, German transcatheter aortic valve interventions registry i. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve interventions registry. *Heart.* 2011;97:899-906.

17. Schultz CJ, Moelker A, Piazza N, Tzikas A, Otten A, Nuis RJ, Neefjes LA, van Geuns RJ, de Feyter P, Krestin G, Serruys PW, de Jaegere PP. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J.* 2010;31:849-856.

18. Tops LF, Wood DA, Delgado V, Schuijf JD, Mayo JR, Pasupati S, Lamers FP, van der Wall EE, Schalij MJ, Webb JG, Bax JJ. Noninvasive evaluation of the aortic root with multislice computed tomography implications for transcatheter aortic valve replacement. *JACC Cardiovasc Imaging.* 2008;1:321-330.

Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

Transcatheter aortaklep implantatie (TAVI) betreft een nieuwe minimaal invasieve behandeling waarbij de aortaklep wordt vervangen zonder dat een open-hart operatie, gebruik van een hart-long machine en stilleggen van het hart nodig is. De ingreep is minder ingrijpend voor de patiënt en wordt in het bijzonder uitgevoerd bij oudere patiënten met een verhoogd risico voor een open-hart operatie. Dit proefschrift draagt bij aan nieuwe inzichten in de huidige en toekomstige rol van TAVI voor de behandeling van aortaklep stenose in oudere, hoog risico patiënten aan de hand van een evaluatie van de frequentie, pathofysiologie en prognostische effecten van complicaties die karakteristiek zijn voor TAVI.

DEEL I. Behandelingskeuze, complicaties en het effect van ervaring.

In hoofdstuk 2 bleek dat ongeveer twee derde van de patiënten dat werd verwezen voor een eventuele TAVI daadwerkelijk deze behandeling onderging en dat bij 7% een chirurgische klepvervanging werd verricht terwijl 28% werd behandeld met medicamenteuze therapie zonder klepvervanging. Redenen om af te zien van TAVI en te kiezen voor ofwel een chirurgische klepvervanging ofwel medicamenteuze therapie waren de voorkeur van de patiënt (29%), perifeer arterieel vaatlijden (15%) en niet-significante aortaklep stenose (11%). Ondanks dat een directe vergelijking tussen de effecten van bovengenoemde behandelingsopties niet mogelijk is gezien het een niet-gerandomiseerd onderzoek betreft, ondersteunen de resultaten dat TAVI gepaard gaat met een betere overleving dan medicamenteuze therapie op 6 maanden, 1 jaar en 2 jaar. Daarnaast bevestigt dit onderzoek de slechte prognose van patiënten die medicamenteuze behandeling zonder klepvervanging ondergaan (TAVI of chirurgische klep vervanging).

Hoofdstuk 3 bestaat uit een gedetailleerd overzicht van de verschillende complicaties die kunnen optreden tijdens en na TAVI. In dit onderzoek bleek dat ≥1 cardiovasculaire en/of niet-cardiovasculaire complicatie voorkwam bij 51% van de patiënten en dat daarnaast een permanente pacemaker nodig was bij 8% terwijl TAVI ongecompliceerd was in 41% van de patiënten. Patiënten met een complicatie en/of een pacemaker implantatie hadden een mediane hospitalisatieduur van 14 dagen. Dit was een twee keer zo langdurige opnametijd als bij patiënten die een ongecompliceerd beloop hadden.

Gezien het korte bestaan van TAVI (sinds 2002) en de toepassing ervan in oudere hoog-risico patiënten die ongeschikt worden bevonden voor een chirurgische klepvervanging zal de veiligheid en effectiviteit van TAVI met name worden bepaald door patiënt-gerelateerde factoren, de TAVI ervaring van de clinicus, en de ontwikkelingen in de technologie en techniek. In hoofdstuk 4 worden de resultaten van TAVI vergeleken vóór en na certificering om TAVI in het Erasmus MC uit te voeren (zonder de aanwezigheid van een proctor). Aanvankelijk werd TAVI uitgevoerd in een experimentele situatie waarbij de procedure werd gekenmerkt door complexe handelingen en technieken. Door een toenemende ervaring en bekendheid met de procedure is de techniek mettertijd in belangrijke mate vereenvoudigd wat heeft geleid tot een afname in de frequentie en de ernst van complicaties. Ondanks

deze positieve ontwikkeling zal TAVI net als elke andere interventie/operatie bij een belangrijk deel van de patiënten gepaard blijven gaan met complicaties.

DEEL II. Frequentie, pathofysiologie en persistentie van nieuwe geleidingsvertraging.
Het optreden van een nieuw linker bundeltak blok en/of compleet atrioventriculair blok vormt een frequente complicatie tijdens en na TAVI en leidt vaak tot de implantatie van een permanente pacemaker. Het optreden van deze typen geleidingsvertraging komt vaker voor na de implantatie van de zelf-expandeerbare Medtronic CoreValve klep dan de ballon-expandeerbare Edwards Sapien klep (tot, respectievelijk, 65 en 27%). Hoofdstuk 5 betreft een artikel waarbij met behulp van een continue 12-afleidingen ECG analyse werd gevonden dat meer dan 80% van de patiënten een nieuwe geleidingsvertraging ontwikkelt tijdens of na TAVI waarvan 75% persisteert tot aan het ontslag van de patiënt. Tevens bleek dat meer dan de helft van de nieuwe geleidingsvertragingen optreedt tijdens de ballon dilatatie van de natieve aortaklep (vóór klepimplantatie) en dat patiënten met een nieuwe geleidingsvertraging tijdens deze fase van de procedure een grotere ballon-annulus ratio hadden dan patiënten die op dat moment geen nieuwe geleidingsvertragingen ontwikkelden. De associatie tussen, enerzijds, het optreden van een nieuwe geleidingsvertraging tijdens de ballon dilatatie en, anderzijds, het optreden van een nieuwe geleidingsvertraging bij patiënten met een grotere ballon-annulus ratio, suggereert dat geleidingsvertragingen voorkomen kunnen worden door een ballon-annulus ratio te kiezen van ≤1.0. Hoofdstuk 6 toont aan dat nieuwe peri-operatieve geleidingstoornissen die persisteren tot aan het ontslag van de patiënt ook persisteren tot 6 maanden na TAVI en om die reden beschouwd kunnen worden als een nieuwe permanente geleidingsvertraging.

DEEL III. Frequentie en pathofysiologie van cerebrovasculaire complicaties.
In Hoofdstuk 8 vonden wij dat een cerebrovasculaire complicatie (CVA/TIA) voorkomt bij 9% van de patiënten en dat meer dan de helft van deze complicaties ≥24 uur na de procedure optreedt. De CT resultaten van het brein toonden dat de cerebrovasculaire complicatie werd veroorzaakt door een corticaal infarct in de meeste patiënten (42%) en een lacunair infarct in 26%. Het post-operatief optreden van (nieuw) atrium fibrilleren was geassocieerd met een 4-voudig verhoogd risico op een cerebrovasculaire complicatie. Alle patiënten die ≥24 uur na TAVI een cerebrovasculaire complicatie ontwikkelden hadden ≥1 episode van atrium fibrilleren doorgemaakt vóór of tijdens het optreden van de cerebrovasculaire complicatie. Echter, geen van deze patiënten had anticoagulantia toegediend gekregen. In lijn met deze resultaten vonden wij in een soortgelijk artikel - gebaseerd op data van 5 ziekenhuizen (Hoofdstuk 9) - dat een cerebrovasculaire complicatie voorkomt bij 5.1% van de patiënten en dat ongeveer de helft van deze complicaties ≥24 uur na de procedure optreedt. Onafhankelijke determinanten van een acute (<24 uur) cerebrovasculaire complicatie waren ballon dilatatie van de klepprothese direct na implantatie en klepprothese embolisatie/migratie. Nieuw atrium fibrilleren was een voorspeller voor cerebrovasculaire complicaties die ≥24 uur na TAVI ontstaan. Daarnaast werd bij 3.1% van de patiënten tijdens

de follow-up periode (>30 dagen na de TAVI) een “laat” cerebrovasculair event vastgesteld. Onafhankelijk voorspellers van late events waren chronisch atrium fibrilleren, perifeer arterieel vaatlijden en een voorgeschiedenis van cerebrovasculaire infarcten. Naast de invaliderende effecten van cerebrovasculaire complicaties op de kwaliteit van leven van de patiënt, bleek er een belangrijke associatie te zijn met mortaliteit op de korte en lange termijn na TAVI.

Het feit dat ongeveer de helft van de cerebrovasculaire complicaties ≥24 uur na de procedure optreedt en dat er een associatie bestaat met nieuw atrium fibrilleren suggereert dat – in bepaalde patiënten – er geen directe relatie bestaat tussen de TAVI procedure zelf en het ontstaan van een cerebrovasculaire complicatie, en dat klinische meer dan technische of procedure-gerelateerde factoren een belangrijkere rol spelen bij het ontstaan van peri-operatieve cerebrovasculaire complicaties. Het is om die reden mogelijk dat preventieve maatregelen met name gericht zouden moeten worden op het post-operatieve traject en dat endovasculaire beschermingsmiddelen die gebruikt worden tijdens de TAVI procedure niet alle cerebrovasculaire complicaties kunnen voorkomen. Daarnaast moet nog blijken of endovasculaire beschermingsmiddelen die gepositioneerd worden in de grote halsvaten op een veilige en effectieve wijze kalk en trombo-embolische deeltjes kunnen opvangen en het aantal cerebrovasculaire events kunnen verminderen. Dit is temeer de vraag aangezien een kwart van de cerebrovasculaire complicaties wordt veroorzaakt door een lacunair infarct waarvan bekend is dat deze ontstaan door cerebrale hypoperfusie bij pre-existent lokale atherosclerose en niet door trombo-embolische occlusie van de cerebrale bloedvaten. Dit suggereert dat de hemodynamische circulatie tijdens TAVI procedures optimaal gehandhaafd moet blijven om cerebrale hypoperfusie te voorkomen.

DEEL IV. Frequentie en pathofysiologie van acuut nierfalen.

In Hoofdstuk 10 vonden wij dat 19% van de patiënten acuut nierfalen ontwikkelt na TAVI en dat 2% tijdelijk nierdialyse behoeftig wordt. Het gebruik van peri-operatieve bloedtransfusies bleek een belangrijke voorspeller voor het optreden van acuut nierfalen, terwijl acuut nierfalen op haar beurt onafhankelijk was geassocieerd met mortaliteit op de korte en lange termijn. De relatie tussen bloedtransfusie en het optreden van acuut nierfalen is in meer detail onderzocht in een grotere populatie in Hoofdstuk 11. In dit onderzoek vonden wij dat acuut nierfalen voorkwam bij 21% van de patiënten. Opnieuw bleek dat bloedtransfusie de belangrijkste voorspeller was voor het optreden van acuut nierfalen. Potentieel uitlokkende factoren die de kans op een bloedtransfusie vergroten zoals pre-operatieve anemie, bloedings- en vasculaire complicaties en peri-operatief bloedverlies werden niet geassocieerd met het optreden van acuut nierfalen. Wel bleek dat patiënten met een ernstige pre-operatieve anemie 2.4 keer minder bloedverlies en 2.3 keer meer bloedtransfusies hadden dan patiënten zonder anemie. Deze resultaten suggereren dat er (mogelijk onbewust) een betere controle bestaat met minder bloedverlies bij patiënten met (ernstige) pre-operatieve anemie en/of dat er een lagere drempel bestaat om transfusies toe te dienen bij deze patiëntengroep. Ten aanzien van de prognostische

effecten bleek dat zowel acuut nierfalen als ernstige bloedingen belangrijke voorspellers waren voor vroege mortaliteit terwijl bloedtransfusie, pre-operatieve anemie en acuut nierfalen belangrijke voorspellers waren voor mortaliteit tijdens de follow-up periode. De klinische boodschap van dit onderzoek vertaalt zich in het mogelijk verbeteren van de uitkomsten na TAVI door een (meer) terughoudend beleid te hanteren ten aanzien van het gebruik van bloedtransfusie therapie.

Deel V. Effecten van pre-operatieve anemie en bloedtransfusie therapie.

In Hoofdstuk 12 bleek dat de prevalentie van pre-operatieve anemie in TAVI patiënten 57% is en dat dit hoger is dan bij andere patiëntgroepen die op hogere leeftijd een cardio-chirurgische interventie ondergaan (tot 36%). Onafhankelijke determinanten van pre-operatieve anemie waren – in volgorde van odds ratio - pre-operatieve mitralisklep insufficiëntie, een voorgeschiedenis van hartfalen, diabetes, mannelijk geslacht, perifeer arterieel vaatlijden en body mass index. Terwijl anemie als een binaire variabele een zwakke associatie had met vroege mortaliteit, bleek dat de ernst van de anemie de belangrijkste voorspeller was voor mortaliteit op de lange termijn met een hazard ratio van 2.92 (95% betrouwbaarheidsinterval: 1.66-5.13) op 1 jaar na TAVI. Bovendien bleek dat patiënten met anemie ongeveer twee keer vaker ≥1 bloedtransfusie ondergingen in vergelijking met patiënten die geen anemie hadden en dat bloedtransfusie een voorspeller was voor zowel vroege als late mortaliteit. Of pre-operatieve correctie van anemie en/of een terughoudend beleid ten aanzien van bloedtransfusie therapie een positief effect zal hebben op de uitkomsten na TAVI dient onderzocht te worden in een gerandomiseerd onderzoek.

Toekomst uitdagingen

De klinische toepassing van een katheter gebonden aortaklep implantatie via een perifeer bloedvat werd voor het eerst uitgevoerd door Alain Cribier in 2002 in Frankrijk. Deze gebeurtenis typeert het innovatieve vermogen van de mensheid om binnen een uitzonderlijk korte maar intensieve periode tot de ontwikkeling te komen van een katheter gebonden hartklepprothese die toepasbaar is in de klinische praktijk.

Dat dit concept klinisch toepasbaar zou worden en voordelen zou bieden voor patiënten, werd aanvankelijk door de een betwijfeld en door de ander met enthousiasme ontvangen. Uiteindelijk heeft de wereldwijde exponentiele toename in het aantal procedures en TAVI instituten reeds vóór de publicatie van gerandomiseerde onderzoeken (TAVI versus chirurgische klepvervanging versus conservatieve therapie) de toekomst van TAVI bepaald. Geschat wordt dat vandaag de dag ongeveer 75.000 patiënten in 500 instituten wereldwijd een TAVI hebben ondergaan. Dit aantal patiënten staat in schril contrast met het aantal patiënten dat is geïncludeerd binnen gerandomiseerd onderzoek waarvan de resultaten gepubliceerd zijn in een peer-review medisch tijdschrift (PARTNER A & B, in totaal 1057 patiënten). Het is om die reden gerechtvaardigd om te stellen dat TAVI een vergelijkbare toekomst zal hebben als percutane coronaire interventie zoals eerder voorspeld door M. Mack.

De data van de PARTNER onderzoeken hebben aangetoond dat patiënten die TAVI ondergaan inderdaad voordeel hebben van de procedure ten aanzien van overleving en kwaliteit van leven. Deze onderzoeken maakten gebruik van een TAVI technologie die volgens huidige maatstaven als “verouderd” kan worden beschouwd gezien de grote dimensies van de toen gebruikte katheters. Met de huidige klinische applicatie van verfijnde katheters en het toekomstig gebruik van verder geavanceerde systemen en klepprothesen lijkt de toekomst van TAVI met betrekking tot de klinisch toepasbaarheid eenvoudig te voorspellen. Echter, TAVI blijft een invasieve procedure die wordt toegepast in patiënten met een verkalkte aortaklepstenose en derhalve gepaard gaat met belangrijke risico’s. Dit proefschrift beschrijft dat de onderliggende risico’s van TAVI multifactorieel zijn. Er kan onderscheid gemaakt worden tussen patiënt-, procedure/clinicus/instituut-, en materiaal-gerelateerde factoren als oorzaak van de complicaties. Hoewel deze factoren het ontstaan van een complicatie kunnen voorspellen op basis van statistische methoden zoals toegepast in dit proefschrift (multivariabele analyses), kunnen conclusies met betrekking tot het onderliggend oorzakelijk verband niet worden gevormd.

Ongeacht de reden van de associatie tussen een variabele en een uitkomst zoals vastgesteld in dit proefschrift, is het duidelijk dat de uitkomsten na TAVI zullen verbeteren met verdere verfijning van katheters. Aanvankelijk werd TAVI uitgevoerd met katheters van 24/25 Fr (transfemoraal) en 33 Fr (transapicaal), terwijl de huidige diameters, respectievelijk, 16 en 24 Fr zijn. Katheters van 14 Fr zullen binnenkort beschikbaar zijn. Aangezien de reductie van de diameter van de katheter zal bijdragen aan een afname van de ernst en het aantal bloedings- en vasculaire complicaties zal – indirect - een afname te verwachten zijn in mortaliteit en andere complicaties zoals acuut nierfalen.

De reductie van het aantal cerebrovasculaire complicaties na TAVI kan worden bereikt door adequate behandeling van (nieuw) atrium fibrilleren en eventueel het gebruik van endovasculaire beschermingsmiddelen waarmee trombo-embolische deeltjes worden opgevangen tijdens de procedure. Het moet nog blijken of dergelijke filters werkelijk het aantal cerebrovasculaire complicaties kan verminderen. Om die reden is in Rotterdam een gerandomiseerd onderzoek opgezet (CLARET).

Het ontstaan van nieuwe intraventriculaire geleidingsvertraging kan worden tegengegaan aan de hand van geoptimaliseerde controle van katheters en klepprothesen tijdens de positionering en ontplooiing. De TAVI ervaring van de clinicus lijkt een beperkte rol te spelen, maar verbeteringen in de ergonomie van de katheters en het gemotoriseerd ontplooien van de klepprothese zal mogelijk bijdragen. De vraag is of nieuwe software applicaties kunnen bijdragen aan het beter positioneren van de klepprothese door de basis van de linker ventrikel uitstroomzone op continue wijze te definiëren op een angiogram. Zo mogelijk hebben de bovengenoemde factoren tezamen een positieve invloed op het optreden van de geleidingsvertragingen tijdens en na TAVI. De meeste winst valt echter te verwachten bij verdergaande ontwikkelingen in het ontwerp en de functie van de frames van de klepprothesen. De ontwikkeling van een volledig herpositioneerbare en uitneembare

prothese is momenteel gaande en het prototype van een dergelijke klep is inmiddels beschikbaar (Portico, ST Jude, Minneapolis, USA).
Verbeteringen in het ontwerp van de klepprothesen zijn daarnaast van belang voor het tegengaan van paravalvulaire aortaklep lekkage. Naast een optimale positie is een extra rok rond de instroomregio van de prothese aangebracht bij de ballon-expandeerbare klep (Edwards LifeSciences). Een dergelijke wijziging in het ontwerp kan een essentieel verschil maken aangezien de kalk van de natieve aortaklep niet wordt verwijderd tijdens TAVI waardoor een complete ontplooiing van het frame van de klepprothese kan worden verhinderd. Hierdoor kan lekkage optreden langs de randen van de prothese. Daarnaast zal de ontwikkeling van 3-dimensionale beeldvorming bruikbaar zijn voor de optimalisatie van patiënten selectie en pre-operatieve planning/voorbereiding.
De cyclus van modificaties in het ontwerp, de toenemende ervaring, het continueren van klinisch onderzoek waarbij de rol van TAVI wordt geobjectiveerd ten op zichte van chirurgische klep vervanging en – in het bijzonder – het continueren van observationeel onderzoek aan de hand van grote patiëntcohorten waarbij de “werkelijk TAVI patiënt” het onderwerp van onderzoek betreft, zal bijdragen aan een gecontinueerde verbetering in de uitkomsten van TAVI. Deze cyclus biedt daarbij ruimte voor nieuwe voorstellen ten aanzien van verbetering van patiënten selectie, de procedure zelf, het post-operatieve traject en het ontwerp van aankomende generaties katheters en klepprothesen. Kritische evaluatie aan de hand van klinisch wetenschappelijk onderzoek zal de toekomst van TAVI stimuleren ten behoeve van patiënten met hartklepziekten. De techniek zal niet beperkt blijven tot de aortaklep.

Curriculum Vitae

CURRICULUM VITAE

Rutger-Jan Nuis was born on November 17th, 1985 in Baarn, The Netherlands. After graduating from secondary school in 2004 (Atheneum, CSW, Middelburg), he spent a gap year in Australia, New Zealand and Sri Lanka. In 2005 he started Medical School at the Erasmus University Medical Center. During the second year, he commenced with the Master of Science in Clinical Research coordinated by the Netherlands Institute of Health Sciences, Rotterdam, Netherlands, with summer sessions at the Johns Hopkins University School of Public Health, Baltimore, USA. He obtained the MSc degree in 2010.

In 2009 he graduated from the preclinical years of Medical School and started a 1-year research period in the transcatheter valve program at the Cardiology Department of the Erasmus Thoraxcenter under supervision of Prof.dr. P.P.T. de Jaegere. In 2010, he postponed his clinical years of Medical School by 6 months to conduct clinical research in the Colombian TAVI program. He started his medical internships in 2011 and obtained the MD degree in 2013. By that time, he obtained a PhD degree in Interventional Cardiology with the thesis entitled: "Transcatheter aortic valve implantation: current results, insights & future challenges", under supervision of Prof.dr. P.P.T. de Jaegere and Prof.dr. F Zijlstra. During the same period he spent a 3 month clinical rotational at the Emergency Department of the Jewish General Hospital at McGill University, Montreal, Canada, and passed step 1 of the United States Medical Licensing Examination (USMLE).

In September 2013 he will start his residency at the Department of Cardiology in the Erasmus Thoraxcenter, Rotterdam, The Netherlands.

PhD Portfolio

PHD PORTFOLIO

Name PhD student:	Rutger-Jan Nuis
Department:	Cardiology
Research school:	Cardiovascular Research School Erasmus University Rotterdam
Title thesis:	Transcatheter Aortic Valve Implantation: Current Results, Insights & Future Challenges
Promotors:	Prof.dr. P.P.T. de Jaegere Prof.dr. F. Zijlstra
Date of thesis defence:	June 11th, 2013

EDUCATION AND DEGREES

2009-2013	PhD Interventional Cardiology Erasmus Medical Center, COEUR PhD Program, Rotterdam
2013	USMLE Step 1 score 215 / 80 United States Medical Licensing Examination (USMLE)
2007-2010	MSc Clinical Research NIHES, Rotterdam, The Netherlands
2005-2012	Doctorate in Medicine and MD / Artsdiploma Erasmus Medical Center, Rotterdam, The Netherlands

TEACHING

2011-2012	Supervising 4th year medical student performing clinical research and writing research paper Erasmus Medical Center, Rotterdam, The Netherlands
2009-2011	Teaching nurses in TAVI complications Erasmus Medical Center, Rotterdam, The Netherlands
2009-2010	Teaching nurses in cardiac anatomy Erasmus Medical Center, Rotterdam, The Netherlands
2009-2010	Erasmus Academic Research Project (EARP) - teaching fellow medical students in human anatomy and dissection skills Erasmus Medical Center, Rotterdam, The Netherlands
2007-2009	Skills lab – assisting during surgical courses. Erasmus Medical Center, Rotterdam, The Netherlands

EXTRA-CURRICULAR ACTIVITIES

2012-present	Secretary EFFECT foundation - http://www.erasmusmc.nl/effect

	Erasmus Medical Center, Rotterdam, The Netherlands
2010	Rotational Emergency Department
	McGill University, Jewish General Hospital, Montreal, Canada
2006-2010	Student assistant Cardio-Thoracic Surgery Department
	Erasmus Medical Center, Rotterdam, The Netherlands
2005	Rotational General Surgery Department
	Flinders Medical Center, Adelaide, Australia
2005	Rotational Lung Disease Department
	Nagoda General Hospital, Kalutara, Sri Lanka
2004-2005	Travelling Australia, New Zealand, Asia

SYMPOSIA AND CONFERENCES

Oral presentations

2013	V Symposio Internacional de patologia valvular y enfermedad estructural cardiac. Cali, Colombia
2013	EuroPCR Congress Paris, France
2012	European Society of Cardiology Congress (ESC) Munich, Germany
2012	EuroPCR Congress Paris, France
2012	V Symposio Internacional de Patología Valvular y enfermedad estructural cardiac. Cali, Colombia
2011	IV Symposio Internacional de patologia valvular y enfermedad estructural cardiac. Cali, Colombia
2011	Dutch society of cardiology (NVVC) Spring Congress Arnhem, Netherlands
2011	COEUR Annual PhD-Day Leiden, Netherlands
2011	EuroPCR Congress Paris, France
2010	Dutch society of cardiology (NVVC) Spring Congress Arnhem, Netherlands
2010	EuroPCR Congress Paris, France
2009	Dutch society of cardiology (NVVC) Autumn Congress Amsterdam, Netherlands

Poster presentations

2013	EuroPCR Congress Paris, France
2012	EuroPCR Congress Paris, France
2012	Transcatheter Therapeutics (TCT) Miami, Florida, USA
2012	Transcatheter Therapeutics (TCT) Miami, Florida, USA
2012	Transcatheter Therapeutics (TCT) Miami, Florida, USA
2012	European Society of Cardiology Congress (ESC) Munich, Germany
2012	European Society of Cardiology Congress (ESC) Munich, Germany
2011	EuroPCR Congress Paris, France
2011	M3 MIRS, Masters In Repair Structural Heart Disease Miami, Florida, USA
2011	M3 MIRS, Masters In Repair Structural Heart Disease Miami, Florida, USA
2011	M3 MIRS, Masters In Repair Structural Heart Disease Miami, Florida, USA
2011	M3 MIRS, Masters In Repair Structural Heart Disease Miami, Florida, USA
2011	M3 MIRS, Masters In Repair Structural Heart Disease Miami, Florida, USA
2011	Transcatheter Therapeutics (TCT) San Francisco, USA
2011	Transcatheter Therapeutics (TCT) San Francisco, USA
2010	EuroPCR Congress Paris, France
2009	American Heart Association, Scientific Sessions Orlando, Florida, USA

MSC CLINICAL RESEARCH COURSE TYPES	COURSE	DATE	ECTS
Erasmus Summer Programme	Principles of Research in Med. and Epid.	Aug-07	0,7
	Introduction to Data-analysis	Sep-08	1
	Regression Analysis	Sep-08	1,9
	Methods of Clinical Research	Aug-07	0,7
	Clinical Trials	Aug-07	0,7
	Topics in Meta-analysis	Feb-08	0,7
	Pharmaco-epidemiology	Aug-07	0,7
	Survival Analysis	Sep-08	1,9
	Case-control Studies	Aug-07	0,7
	Introduct.to Decision-making in Medicine	Aug-07	0,7
Core courses	Study Design	Jan-08	4,3
Programme specific Courses	Broad orientation - 2nd year elective	Feb-10	5
	Modern Statistical Methods	Dec-08	4,3
Advanced courses	Introduction to Clinical Research	Feb-08	0,9
	Adv.Topics in Decision-making in Med.	Feb-08	1,9
	Pharmaco-epidemiology and Drug Safety	Apr-10	1,9
	Intervention Research and Clinical Trial	Feb-08	0,9
	Diagnostic Research (EWP05)	Feb-08	0,9
	Advanced Topics in Clinical Trials	Feb-10	1,9
	Advanced Analysis of Prognosis Studies	Feb-10	0,9
	Prognosis Research (EWP16)	Feb-08	0,9
	Princ.of Epidemiologic Data-analysis	Feb-10	0,7
	Ethnicity, Health and Health Care	Mrch-08	1,1
	Research Themes and Methodologies A	Feb-08	1
	Research Seminars 1	Jun-10	3
	Research Seminars 2	Jun-10	3
	Harvard or Johns Hopkins	Jul-09	4
	Vascular Clinical Epidemiology	Mrch-10	1,5
	Cardiovascular Imaging and Diagnostics	Apr-10	1,5
Skills courses	Working with SPSS for Windows	Feb-08	0,15
	A First Glance at SPSS for Windows	Feb-08	0,15
	Scientific Writing in Eng. for Publ.	Dec-09	2

Research	Research Period	Mey-10	60,7
	Research Period 2	Jan-11	25
Extra-curricular	Development Research Proposal	Jan-09	11
TOTAL ECTS			**148,3**

GRANTS / PRIZES

1. EuroPCR 2nd Best Oral Presentation – Blood Transfusion and the Risk of Acute Kidney Injury after Transcatheter Aortic Valve Implantation. EuroPCR congress, May 2013, Paris, France.

2. Award Best Oral Presentation - In-Hospital Complications And Length Of Stay After Transcatheter Aortic Valve Implantation. Dutch society of cardiology, October 2009, Amsterdam, Netherlands

3. Award Best Oral Presentation - Timing and Potential Mechanisms of New Conduction Abnormalities during the Implantation of the Medtronic CoreValve System in Patients with Aortic Stenosis. COEUR PhD-Day, April 15, 2011, Leiden, Netherlands

4. Grant Erasmus-Columbus European Union Research Foundation for the purpose of research in the Colombian TAVI Program from September 2010 to February 2011 (www.erasmus-columbus.eu)

5. Gold Award Presentation - Timing and Potential Mechanisms of New Conduction Abnormalities during the Implantation of the Medtronic CoreValve System in Patients with Aortic Stenosis. M3 MIRS, October 5, 2011, Miami, Florida, USA

6. Gerrit Jan Mulder Award 2011 – Best research thesis Erasmus University Medical Center. February 24, 2012, Rotterdam, Netherlands

List of publications

LIST OF PUBLICATIONS

1. **Nuis RJ**, Piazza N, Van Mieghem NM, Otten AM, Tzikas A, Schultz CJ, van der Boon R, van Geuns RJ, 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*. 2011;78:457-467.

2. **Nuis RJ**, Van Mieghem NM, Tzikas A, Piazza N, Otten AM, Cheng J, van Domburg RT, Betjes M, Serruys PW, de Jaegere PP. Frequency, determinants, and prognostic effects of acute kidney injury and red blood cell transfusion in patients undergoing transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2011;77:881-889.

3. **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. Timing and potential mechanisms of new conduction abnormalities during the implantation of the Medtronic CoreValve System in patients with aortic stenosis. *Eur Heart J.* 2011;32:2067-2074.

4. **Nuis RJ**, van Mieghem NM, van der Boon RM, van Geuns RJ, 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.

5. **Nuis RJ**, Dager AE, van der Boon RM, 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.* 2012;20:16-23.

6. **Nuis RJ**, Van Mieghem NM, Schultz CJ, Moelker A, van der Boon RM, van Geuns RJ, van der Lugt A, Serruys PW, Rodes-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.

7. **Nuis RJ**, Rodes-Cabau J, Sinning JM, van Garsse L, Kefer J, Bosmans J, Dager AE, van Mieghem N, Urena M, Nickenig G, Werner N, Maessen J, Astarci P, Perez S, Benitez LM, Dumont E, van Domburg RT, de Jaegere PP. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. *Circ Cardiovasc Interv.* 2012;5:680-688.

8. **Nuis RJ,** van der Boon R, Van Mieghem N, Nauta ST, van Domburg R, Serruys PW, Jordaens L, de Jaegere PP. Defective Recovery of QT Dispersion Following Transcatheter Aortic Valve Implantation. *Submitted.*

9. **Nuis RJ,** Sinning JM, Rodés-Cabau J, Gotzmann M, van Garsse L, Kefer J, Bosmans J, Yong G, Dager AE, Revilla-Orodea A, Urena M, Nickenig G, Werner N, Maessen J, Astarci R, Perez S, Benitez LM, Amat-Santos IJ, López J, Dumont E, van Domburg R, van Mieghem N, van Gelder T, de Jaegere PP. Prevalence and Effects of Pre-Operative Anemia on Short- and Long-term Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation. *Submitted.*

10. **Nuis RJ**, de Jaegere P. Electrocardiographic and further predictors for permanent pacemaker requirements after transcatheter aortic valve implantation. *Europace.* 2010;12:1061-1062.

11. **Nuis RJ**, Benitez LM, Nader C, Perez S, de Marchena E, Dager AE. Valve-in-Valve-in-Valve TAVI for the treatment of a degenerated surgical bioprosthesis in sub-aortic position. *Tex Heart Inst J 2013. Accepted.*

12. Van Mieghem N, **Nuis RJ**, Piazza N, Apostolos T, Ligthart J, Schultz C, de Jaegere PP, Serruys PW. Vascular complications with transcatheter aortic valve implantation using the 18 Fr Medtronic CoreValve System: the Rotterdam experience. *EuroIntervention.* 2010;5:673-679.

13. Otten AM, **Nuis RJ**, van Domburg RT, Koudstaal PJ, Piazza N, van Geuns RJ, Kappetein AP, Bogers AJ, Serruys PW, de Jaegere PP. Survival and disorders after percutaneous aortic valve replacement. *Ned Tijdschr Geneeskd.* 2010;154:A529.

14. Piazza N, **Nuis RJ**, Tzikas A, Otten A, Onuma Y, Garcia-Garcia H, Schultz C, van Domburg R, van Es GA, van Geuns R, de Jaegere P, Serruys PW. Persistent conduction abnormalities and requirements for pacemaking six months after transcatheter aortic valve implantation. *EuroIntervention.* 2010;6:475-484.

15. Van Mieghem N, **Nuis RJ**, Tzikas A, Piazza N, Schultz C, Serruys PW, de Jaegere PP. Prevalence and prognostic implications of baseline anaemia in patients undergoing transcatheter aortic valve implantation. *EuroIntervention.* 2011;7:184-191.

16. Dager AE, **Nuis RJ**, Caicedo B, Fonseca JA, Arana C, Cruz L, Benitez LM, Nader CA, Duenas E, de Marchena EJ, O'Neill WW, de Jaegere PP. Colombian experience with transcatheter aortic valve implantation of medtronic CoreValve. *Tex Heart Inst J.* 2012;39:351-358.

17. van der Boon R, **Nuis RJ**, Van Mieghem NM, Benitez LM, van Geuns RJ, 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.* 2012;79:702-710.

18. van der Boon R, **Nuis RJ**, Van Mieghem NM, Jordaens L, Rodes-Cabau J, van Domburg RT, Serruys PW, Anderson RH, de Jaegere PP. New conduction abnormalities after TAVI--frequency and causes. *Nat Rev Cardiol.* 2012;9:454-463.

19. Van der Boon R, **Nuis RJ**, van Mieghem N, Schultz C, Serruys P, de Jaegere P. Frequency and determinants of Infective complications Following Transcatheter Aortic Valve Implantation. *Am J Cardiol 2013. Accepted.*

20. Nombela-Franco L, Webb JG, de Jaegere PP, Toggweiler S, **Nuis RJ**, Dager AE, Amat-Santos IJ, Cheung A, Ye J, Binder RK, van der Boon RM, Van Mieghem N, Benitez LM, Perez S, Lopez J, San Roman JA, Doyle D, Delarochelliere R, Urena M, Leipsic J, Dumont E, Rodes-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.

21. van der Boon RM, Van Mieghem NM, Theuns DA, **Nuis RJ**, Nauta ST, Serruys PW, Jordaens L, van Domburg RT, de Jaegere PP. Pacemaker dependency after transcatheter aortic valve implantation with the self-expanding Medtronic CoreValve System. *Int J Cardiol.* [Ahead of print].

22. Van Mieghem NM, van der Boon RM, **Nuis RJ**, Schultz C, van Geuns RJ, Serruys PW, Kappetein AP, van Domburg RT, de Jaegere PP. Cause of death after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2012.

23. Schultz C, Ali O, Jabbour A, **Nuis RJ**, van Mieghem N, Rubens M, Davies S, DiMario C, van der Boon R, Dalby M, Moat N, de Jaegere PP. Under sizing of the Medtronic Corevalve prosthesis is associated with early mortality. *Submitted.*

24. Schultz CJ, Tzikas A, Moelker A, Rossi A, **Nuis RJ**, Geleijnse MM, van Mieghem N, Krestin GP, de Feyter P, Serruys PW, de Jaegere PP. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the Medtronic CoreValve prosthesis. *Catheter Cardiovasc Interv.* 2011;78:446-455.

25. Schultz CJ, Papadopoulou SL, Moelker A, **Nuis RJ**, Ten Kate GJ, Mollet NR, Geleijnse ML, de Feyter P, de Jaegere P, Serruys PW. Transaortic flow velocity from dual-source MDCT for the diagnosis of aortic stenosis severity. *Catheter Cardiovasc Interv.* 2011;78:127-135.

26. Van Mieghem NM, Schultz CJ, van der Boon RM, **Nuis RJ**, Tzikas A, Geleijnse ML, van Domburg RT, Serruys PW, de Jaegere PP. Incidence, timing, and predictors of valve dislodgment during TAVI with the Medtronic Corevalve System. *Catheter Cardiovasc Interv.* 2012;79:726-732.

27. Tzikas A, Piazza N, Geleijnse ML, Van Mieghem N, **Nuis RJ**, Schultz C, van Geuns RJ, Galema TW, Kappetein AP, Serruys PW, de Jaegere PP. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the medtronic CoreValve system in patients with aortic stenosis. *Am J Cardiol.* 2010;106:255-260.

28. Tzikas A, Piazza N, van Dalen BM, Schultz C, Geleijnse ML, van Geuns RJ, Galema TW, **Nuis RJ**, Otten A, Gutierrez-Chico JL, Serruys PW, de Jaegere PP. Changes in mitral regurgitation after transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2010;75:43-49.

29. Schultz CJ, Moelker A, Piazza N, Tzikas A, Otten A, **Nuis RJ**, Neefjes LA, van Geuns RJ, de Feyter P, Krestin G, Serruys PW, de Jaegere PP. Three dimensional evaluation of the aortic annulus using multislice computer tomography: are manufacturer's guidelines for sizing for percutaneous aortic valve replacement helpful? *Eur Heart J.* 2010;31:849-856.

30. Piazza N, Wenaweser P, van Gameren M, Pilgrim T, Tzikas A, Otten A, **Nuis RJ**, Onuma Y, Cheng JM, Kappetein AP, Boersma E, Juni P, de Jaegere P, Windecker S, Serruys PW. Relationship between the logistic EuroSCORE and the Society of Thoracic Surgeons Predicted Risk of Mortality score in patients implanted with the CoreValve ReValving system--a Bern-Rotterdam Study. *Am Heart J.* 2010;159:323-329.

31. Piazza N, Grube E, Gerckens U, Schuler G, Linke A, den Heijer P, Kovacs J, Spyt T, Laborde JC, Morel MA, **Nuis RJ**, Garcia-Garcia HM, de Jaegere P, Serruys PW. A clinical protocol for analysis of the structural integrity of the Medtronic CoreValve System frame and its application in patients with 1-year minimum follow-up. *EuroIntervention.* 2010;5:680-686.

32. Tzikas A, Geleijnse ML, Van Mieghem NM, Schultz CJ, **Nuis RJ**, van Dalen BM, Sarno G, van Domburg RT, Serruys PW, de Jaegere PP. Left ventricular mass regression one year after transcatheter aortic valve implantation. *Ann Thorac Surg.* 2011;91:685-691.

33. Tzikas A, Schultz CJ, Piazza N, Moelker A, Van Mieghem NM, **Nuis RJ**, van Geuns RJ, Geleijnse ML, Serruys PW, de Jaegere PP. Assessment of the aortic annulus by multislice computed tomography, contrast aortography, and trans-thoracic echocardiography in patients referred for transcatheter aortic valve implantation. *Catheter Cardiovasc Interv.* 2011;77:868-875.

34. Tzikas A, van Dalen BM, Van Mieghem NM, Gutierrez-Chico JL, **Nuis RJ**, Kauer F, Schultz C, Serruys PW, de Jaegere PP, Geleijnse ML. Frequency of conduction abnormalities after transcatheter aortic valve implantation with the Medtronic-CoreValve and the effect on left ventricular ejection fraction. *Am J Cardiol.* 2011;107:285-289.

35. Cheng JM, Onuma Y, Piazza N, **Nuis RJ**, Van Domburg RT, Serruys PW, Interventional Cardiologists of T. Comparison of five-year outcome of octogenarians undergoing percutaneous coronary intervention with drug-eluting versus bare-metal stents (from the RESEARCH and T-SEARCH Registries). *Am J Cardiol.* 2010;106:1376-1381.

36. Van Mieghem NM, Tzikas A, **Nuis RJ**, Schultz C, de Jaegere PP, Serruys PW. How should I treat a staggering TAVI procedure? *EuroIntervention.* 2010;6:418-423.

37. Nauta ST, van Domburg RT, **Nuis RJ**, Akkerhuis M, Deckers JW. Decline in 20-year mortality after myocardial infarction in patients with chronic kidney disease: evolution from the prethrombolysis to the percutaneous coronary intervention era. *Kidney Int.* 2013 [ahead of print].

Dankwoord

DANKWOORD

"Zorg dat je snel weet welke kant je op wil en ga zo snel mogelijk onderzoek doen". Dit was het advies van Vincent Nieuwenhuijs, een Nederlandse chirurg die ik in 2004 in Australië heb leren kennen en die een belangrijke rol heeft gespeeld bij mijn decentrale toelating tot de studie geneeskunde in Rotterdam. Halverwege het eerste jaar viel mijn keus op de cardiologie en een jaar later was ik betrokken bij cardiovasculair onderzoek. De afgelopen jaren heb ik met veel plezier gewerkt aan dit onderzoek en kijk ik terug op een leerzame periode waarvan ik in het begin niet had verwacht dat het zou resulteren in een promotie.

Onderzoek doen tijdens de studie geneeskunde en promoveren tijdens de coschappen is erg leuk en uitdagend, maar had nooit volbracht kunnen worden zonder de bijdrage en steun van collega's, vrienden en familie. Het verschijnen van dit proefschrift biedt mij de gelegenheid om allen te bedanken en enkele personen in het bijzonder te noemen.

Allereerst mijn eerste promotor, Prof.dr. P.P.T. de Jaegere. Beste Peter, graag wil ik jou bedanken voor de plezierige periode waarin je mijn onderzoek hebt begeleid en mij de weg hebt gewezen naar de totstandkoming van dit proefschrift. Grote bewondering heb ik voor jouw manier van werken en hoe jij het TAVI programma in 2005 in het Erasmus MC hebt opgestart en uitgebreid. Sinds die tijd hebben jouw drive, passie en visie ertoe geleid dat het TAVI programma een belangrijke bijdrage heeft geleverd ten aanzien van de ontwikkelingen van deze nieuwe behandelingstechniek. Dit heeft mogen resulteren in jouw benoeming tot hoogleraar en was (voor mij) zonder meer een hoogtepunt. Mijn samenwerking met jou heeft mij op wetenschappelijk, klinisch en persoonlijk vlak gevormd voornamelijk tijdens de vele schrijfsessies waar ik heb geleerd om te denken, schrijven, herdenken en herschrijven. Met regelmaat wilde ik volgens jou "te veel" en riep je mij terug om allereerst één project tegelijk te doen en dat eerst af te ronden om vervolgens zorgvuldig na te denken over een eventueel vervolgonderzoek. We hebben op elk denkbare locatie samengewerkt: op jouw kamer op de 5^{e} verdieping, in het kathlab, in Colombia, op Miami Beach etc. Naast mijn waardering voor jouw manier van werken heb ik bewondering voor jou en Sophie als mens buiten de wereld van het ziekenhuis/onderzoek. Peter, ik ben vereerd om jouw eerste promovendus te mogen zijn en ik kijk uit naar het vervolg van onze samenwerking.

Mijn eerste (email)contact met de cardiologie verliep via Ron van Domburg in het tweede jaar van mijn studie. Ik vroeg hem of ik eens kon komen praten over de mogelijkheden om te helpen bij wetenschappelijk onderzoek: nog geen 2 weken later was ik aan het werk gezet. Beste Ron, mijn copromotor en de statistische "backbone" van dit proefschrift, net als alle andere studenten kon ik de afgelopen jaren bij jou terecht met mijn vragen en – zeer belangrijk – kon ik erop rekenen dat ik binnen 1 dag een bruikbaar antwoord had. Vrijwel altijd sta je positief en enthousiast tegenover nieuwe onderzoeksvoorstellen. Ik heb je laten

weten dat ik interesse had voor de interventiecardiologie waarna je mij bij het TAVI programma hebt geïntroduceerd. Onze samenwerking vond ik altijd prettig en gemakkelijk; ik hoop dat dit in de toekomst voortgezet mag worden. Veel dank.

Prof.dr. F. Zijlstra, graag wil ik u bedanken voor uw optreden als tweede promotor. Prof.dr. H. Boersma, Prof.dr. A.P. Kappetein, Prof.dr. A. Bogers en Prof.dr. H. Suryapranata wil ik graag bedanken voor hun bereidheid zitting te nemen in de kleine promotie commissie en het beoordelen van mijn proefschrift. Dr. A. Balk en Prof.dr. J Bosmans wil ik hartelijk danken voor het zitting nemen in de grote commissie en jullie bereidheid om van gedachten te wisselen over de inhoud van het proefschrift.

Nicolas van Mieghem, wat is het super om samen te werken met jouw eindeloze enthousiasme, je “Ferrari” mentaliteit en je onuitputtelijke ideeënstroom. We kwamen ongeveer tegelijk aan in Rotterdam: ik als student, jij als cardioloog en allebei relatief onwetend en onbekend binnen de onderzoekswereld. Al snel zaten we met Nicolo aan tafel en hadden we een eerste artikel geschreven, wat een snelle en energetische tijd was dat. Ik kijk uit naar de klinische periode die nu voor mij ligt waarin ik veel van jou zal leren.

Robert van der Boon, mijn opvolger met betrekking tot data management; jouw enthousiasme en snelle zelfstandigheid hebben ertoe geleid dat je in korte tijd veel hebt bereikt. Ik kijk met een heel goed gevoel terug op onze samenwerking. Soms moesten we een bureau delen en zaten we bovenop elkaar terwijl op andere momenten de samenwerking via een Skype verbinding verliep tussen Colombia (ik) en Rotterdam (jij). Niet alleen ik, maar ook de Cali groep is je dankbaar voor het werk dat je hebt verricht. Ik ben benieuwd naar je proefschrift.

Amber Otten en Elhamula Faqiri, jullie wil ik bedanken voor de goede maar korte samenwerking. Amber, veel succes met je opleiding; Elham, veel plezier tijdens de coschappen (je zult zien dat het meevalt).

Prof.dr. P.J. Koudstaal, hartelijk dank voor uw inbreng, in het bijzonder ten aanzien van het “stroke artikel”. Ik kan mij goed herinneren dat ik u via de email om raad vroeg en dat ik binnen een week – na een leuke kennismaking met Minah - met u de CT scans van de TAVI patiënten analyseerde. Deze samenwerking was zeer prettig, leerzaam en plezierig.

Apostolos Tzikas, my Greek friend, I remember very well that you and I started in Rotterdam at the same time. After all you made a quick visit to Rotterdam that lasted 2 years where you worked hard on imaging techniques in TAVI and quickly obtained a PhD degree. Thank you for teaching me the basics in echocardiography and taking care of the bills when we had drinks. I wish you, Katharina and Zoi the best of luck in Greece.

Carl Schultz, de imaging man, graag wil ik je danken voor de samenwerking die we hebben gehad. Je vervult een bijzondere rol binnen de ontwikkeling van de beeldvorming voor TAVI en zal dit werk vanaf aankomende zomer voortzetten in Perth, Australië. Ondanks je vertrek zullen we blijven samenwerken. Ik wens je veel succes en plezier.

Nicolo Piazza, thank you for your endless energy to teach me both clinically and scientifically. You were the first person I closely worked with. In a period of months I was able to easily interpret the basics of electrocardiography and coronary angiography. You urged me to purchase textbooks on how to write scientific articles, taught me how to write abstracts and explained me how to deal with statistical analyses in SPSS. In addition, you organized my 2-months clinical rotational at the Emergency Department at McGill University in Montreal, where we also had the great "hotdog-party" with your family. I admire your ambitious personality that has brought you where you currently are. Thank you and Lisa for the multiple Italian dinners at your home in the Veerhaven. Hopefully our collaboration might take a restart in the future.

Anne-Marie Maugenest, graag wil ik jou bedanken voor je interesse en steun bij de TAVI onderzoeken. In het bijzonder heb je een belangrijke rol gespeeld bij het onderzoek waar we de timing van geleidingsvertragingen tijdens TAVI hebben vastgesteld. Het was een grote klus maar zeker de moeite waard!

Marjo, Paul, Rob, Patrick, Linda, Peggy en alle andere verpleegkundigen van het kath lab bedank ik voor de interesse in het onderzoek en jullie uitleg en humor tijdens de TAVI procedures.

Annette Tolhoek, hartelijk dank voor alle voorbereidingen voor de promotie; je was mijn alle-hens-aan-dek en hebt het voor elkaar gekregen om in een (zeer) korte periode de promotie rond te krijgen.

Dear Dr Antonio Dager, my Colombian boss, teacher, friend and support. As a non-Spanish speaking student it was challenging for me to rely on your single email stating that I could spend some time with you in your clinic in Cali for the purpose of the initiation of a Colombian TAVI databank. How could I imagine what to expect in Colombia? Why would this become a success? Although I didn't know the answers to these questions, I decided to just go most probably because of curiosity and adventurous ambitions. My 3-month visit to Cali turned out to be - without any doubt - one of my best experiences: I learned Spanish, "jugaste una partida de billar", I spent many hours in the cathlab, we had daily discussions about each aspect of TAVI, you even relied on my opinion during TAVI cases and organized everything for me. I have great appreciation for your ambition to make the Cali TAVI program a success despite the continuous difficulties you encounter during this process. It

was an honour to work with you and your Angiografia family and I am proud of this fruitful and solid collaboration. Thank you and Martha for everything.

Luis Miguel Benitez and Sergio Pérez, the scientific backbone of the Cali TAVI program, I thank you for your continuous efforts on data management and the endless support for each of the projects we have worked on together. During my stay in Cali you made me feel very welcome, took me out to the best places in town and even invited me to your homes. Luis, I look forward to visit your farm again to enjoy the breathtaking view, your family and great barbecue skills. Sergio, I wish you all the best during you training years in Miami.

To all personnel working in Angiografia de Occidente in Cali, I am very grateful to have worked with all of you. Thank you for making me feel welcome, teaching me Spanish, teaching me Salsa and sharing your great sense of humour.

The following persons from various institutions in- and outside The Netherlands are gratefully acknowledged for their continuous efforts that have led to the completion of this thesis: Drs Jan-Malte Sinning, Georg Nickenig, Nikos Werner (University Hospital Bonn, Germany), Josep Rodes-Cabau, Marina Urena, Eric Dumont (Quebec Heart and Lung Institute, Canada), Michael Gotzmann (Ruhr-University Bochum, Germany), Leen van Garsse, Jos Maessen (University Hospital Maastricht), Joelle Kefer, Parla Astarci (University Hospital Saint-Luc, Brussels, Belgium), Johan Bosmans (University Hospital Antwerp, Antwerp, Belgium), Gerald Yong (Royal Perth Hospital, Perth, Western Australia), Ignacio Amat-Santos, Ana Revilla-Orodea and Javier López (Hospital Clínico Universitario de Valladolid, Spain).

Promoveren tijdens de coschappen kost niet alleen tijd, maar gaat met periodes ook gepaard met enige frustratie. Het voelt dan goed om op je omgeving terug te kunnen vallen. Ik wil daarom mijn vrienden en familie bedanken.

Sjoerd Nauta, ik heb met jou alle onderzoeksjaren op dezelfde kamer gezeten en je weet alle ins en outs van mij als persoon en hoe ik tegen een en ander aankijk. Dankjewel voor het opvangen van mijn commentaar en gezeur, en je bruikbare advies bij mijn onderzoek. Je hebt uitzonderlijk onderzoek verricht en meerdere prijzen in de wacht gesleept. Dit zal zonder twijfel resulteren in een bijzonder proefschrift. Ik kijk uit naar de komende tijd in de kliniek!

Robbert van Onkelen, naast de vele koffie-uren in de faculteit wil ik je ook graag bedanken voor je hulp en advies bij het onderzoek, de Master cursussen en vele opdrachten die gemaakt moesten worden voor de geneeskunde studie waarbij jouw hulp goed van pas kwam omdat ik net een aantal maanden op jou achter liep. Je hebt je promotie zo goed als in de pocket en daarnaast heb je het voor elkaar gekregen om extra-curriculaire cursussen op te zetten voor geneeskunde studenten. Of dat nog niet genoeg is heb je – na veel

obstakels en tegenvallers – het voor elkaar gekregen om stichting EFFECT op te richten. Veel succes met de laatste maanden onderzoek en het afronden van je proefschrift.

Roderick van Klink, dankjewel dat je dit proefschrift een gezicht hebt kunnen gegeven met een mooie kaft. Eén dag vóór het drukken van dit boekje heb ik je om hulp gevraagd en ben je erin geslaagd om een perfecte foto van de Willemsbrug te maken en die zodanig te bewerken totdat je op dit eindproduct kwam.

Bas Ansberg en Hein Smit, bedankt dat jullie mijn paranimfen zijn. Noem een plaats als Eernewoude in Friesland, Krakow in Polen of Corbier in Oostenrijk en héle mooie herinneringen herrijzen. Strijkers, ondanks dat de meesten niet meer in Rotterdam wonen blijft de traditie van 31 december en 30 (of 27) april staan; ik beloof vaker richting 020 te komen.

Lies, jou heb ik tijdens het laatste deel van dit traject ontdekt, een betere afloop van de onderzoeksperiode kan ik niet bedenken. Dankjewel voor het mij op sleeptouw nemen om veel leuke dingen te doen; de vakantie in Champoussin was een hoogtepunt waarvoor ik je familie dankbaar ben!

Tot slot wil ik mijn familie bedanken. Naast de leuke gebeurtenissen die gepaard gaan met studie en onderzoek krijgen ook zij regelmatig te kampen met de nodige onderzoeksfrustraties. Broers, dankjewel voor het voorrijden als ik weer eens weigerde met de trein te gaan. Pap/mam, dank voor jullie steun om altijd te doen wat ik wil, zowel in mijn vrije tijd als op het gebied van studie en promotie. Zonder jullie was dit proefschrift nooit verschenen.