Outcomes of transcatheter aortic valve implantation

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OUTCOMES OF TRANSCATHETER AORTIC VALVE IMPLANTATION

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To my parents and teachers Mixalis and Alexandra

Contents

Chapter 1

General introduction and outline of the thesis

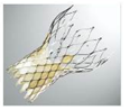
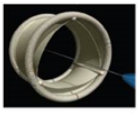
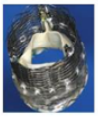
TRANSCATHETER AORTIC VALVE IMPLANTATION: CURRENT STATUS AND CHALLENGES TO IMPROVE OUTCOMES

Degenerative severe aortic valve stenosis is a frequent valvular disease affecting 3% of patients aged>75 years and its prevalence is expected to increase.(1) Elderly patients with symptomatic severe aortic stenosis have poor outcFome if medically treated, whereas surgical aortic valve replacement reduces the 1-year mortality rates significantly.(2,3) However, at least 30% of symptomatic severe aortic stenosis patients are considered of excessive surgical risk and are not referred to or are denied for surgical treatment. (4) Balloon aortic valvulotomy is associated with limited clinical improvement, does not show any prognostic improvement and is associated with high rate of recurrence of aortic stenosis (80% at 1 year follow up).(5,6) Transcatheter aortic valve implantation (TAVI) has been an important therapeutic breakthrough for patients with symptomatic severe aortic stenosis and contraindications for surgical aortic valve replacement.

The first-in-human TAVI was successfully performed in 2002, in a critically ill patient with severe aortic stenosis in whom previous balloon valvulotomy had failed.(7) The prosthesis device and implantation technique were further developed and the results of the cohort B Placement of Aortic TraNscathetER Valves (PARTNER) trial demonstrated that TAVI is a safe and effective treatment for patients with symptomatic severe aortic stenosis and contraindications for surgery, improving the outcome of these patients compared with patients who were conventionally treated (medically or with balloon aortic valvulotomy): 1 year mortality 30.7% vs. 50.7%, respectively.(8) Subsequently, the Food and Drug Administration approved TAVI as an alternative to surgical aortic valve replacement for non-operable patients. The results of the cohort A PARTNER trial, randomizing patients with severe aortic stenosis and high operative risk to TAVI or surgical aortic valve replacement demonstrated that TAVI was also safe in this subgroup of patients and led to comparable outcomes at follow-up (1-year mortality: 24.2% with TAVI vs. 26.8% with surgical treatment).(9) The results of these randomized trials and the numerous national registries have established TAVI as a safe and feasible alternative for patients with symptomatic severe aortic stenosis who are non-surgical candidates or have high surgical risk. Furthermore, TAVI is currently included in the 2012 European Society of Cardiology guidelines for the management of patients with symptomatic severe aortic stenosis and contraindications or high-risk for surgery, with class IB and IIa B indications, respectively.(10)

However, TAVI is also associated with complications. The rate of stroke was higher in the group of patients treated with TAVI compared with surgically treated group.(8,11) Moreover paravalvular aortic regurgitation (AR) was more frequently observed in TAVI compared to surgically treated patients, having important prognostic implications since moderate and severe paravalvular AR were related to increased mortality at follow-up. (11) Patients treated with TAVI also showed a higher rate of new conduction abnormalities

Table 1. Transcathter aortic valve devices

	Device-Company	Expansion mechanism	Valve material	Stent material	Repositionable
	Sapien Edwards	Balloon-expandable	Bovine pericardium	Cobalt Chromiun	No
	CoreValve ReValving system Medtronic	Self-expandable	Porcine Pericardium	Nitinol	No
	Portico	Self-expandable	Bovine Pericardium	Nitinol	No
	CoreValve Evolut R	Self-expandable	Bovine Pericardium	Nitinol	No
	Sapien III	Balloon-expandable	Pericardium	Cobalt Chromiun	Yes
	Direct Flow Direct Flow Medical	Polymer-injected	Equine pericardium	Polymer	Yes
	JenaValve JenaValve Technology	Self-expandable	Pericardium	Nitinol	Yes
	Lotus Sadra Medical	Self-expandable	Bovine pericardium	Nitinol	Yes

and pacemaker implantation compared with surgically treated patients.(12) A number of additional complications of this relatively new procedure that may affect the clinical course of patients were also acknowledged: perioperative myocardial infarction, acute kidney injury, pericardial effusion, vascular and bleeding complications.(13)

The patient characteristics are one of the main determinants of the risk of procedural complications. The rate of the observed complications may also differ between trans-

catheter aortic valve manufacturers. Currently, the balloon-expandable Edwards SAPIEN (Edwards SAPIEN or SAPIEN XT, Edwards Lifescience, Irvine, CA) and the self-expandable CoreValve (CoreValve system, Medtronic, Minneapolis, MN) are widely commercially available although a plethora of new designs have been clinically studied (Table 1).(14)

The Edwards SAPIEN valve can be implanted both through transfemoral and transapical access whereas the CoreValve system is implanted mainly through transarterial access (transfemoral, transsubclavian, transaxillary or direct transaortic). The design of the frames has undergone several modifications in order to optimize its deployment in the aortic root and avoid related complications. The optimal recommended deployment of the frame is not easy to achieve and a shallow or deep implantation of the valve in the left ventricular outflow tract may be observed, which may increase the risk of acute coronary ostia occlusion, paravalvular regurgitation or prosthesis migration.(15) In addition, it is acknowledged that some complications may be expected more frequently in specific transcatheter valve designs. For example, in patients treated with the CoreValve device, pacemaker implantation is more frequent compared with patients treated with the Edwards SAPIEN valve.(14)

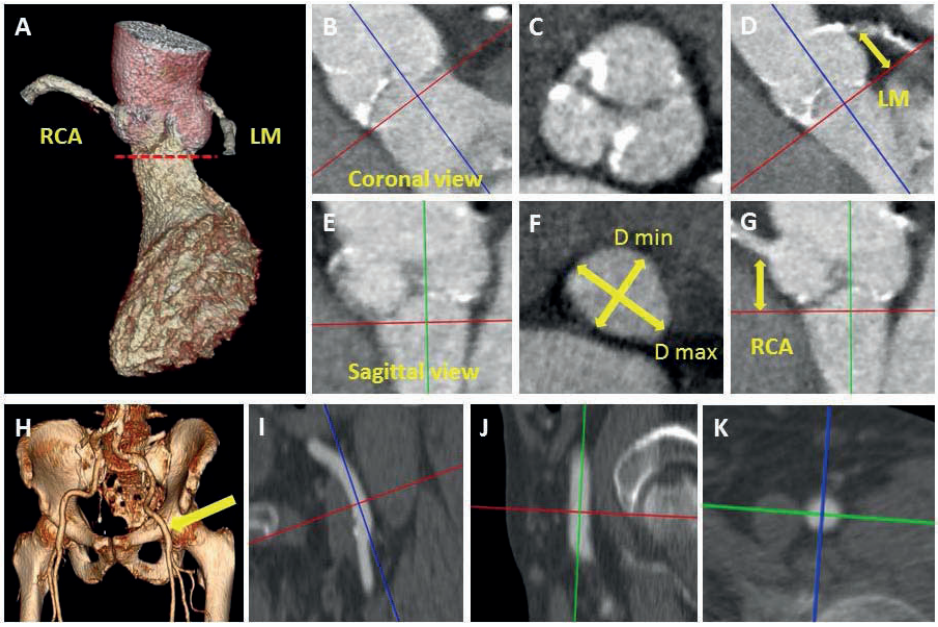
It is becoming apparent that in order to optimize the management of TAVI candidates there should be an emphasis on careful selection of patients that will benefit most from this procedure, in combination with an effort to minimize procedural complications that influence their post-operative clinical course. Consequently, understanding the pathophysiology of TAVI complications and defining the outcome of specific high risk groups may be of clinical importance.

EMERGING ROLE OF MULTI-DETECTOR ROW COMPUTED TOMOGRAPHY TO PREDICT OUTCOMES IN PATIENTS UNDERGOING TRANSCATHETER AORTIC VALVE IMPLANTATION

Multi-detector row computed tomography (MDCT) is an important imaging technique to evaluate patients with symptomatic severe aortic stenosis who are candidates for TAVI. The superb spatial resolution of this imaging technique permits accurate sizing of the aortic annulus, key to select the most appropriate transcatheter valve size. Studies have shown that the choice of valve size based on MDCT measurements, as opposed to echocardiography or angiography measurements, has led to less postoperative paravalvular AR and therefore MDCT is emerging as the ''gold standard'' method for valve sizing in patients undergoing TAVI (Figure 1). (16)

MDCT is also used to asses dimensions of various components of the aortic root such as the height of the coronary ostia relative to the aortic annulus, and moreover it can be used to clarify the size and morphology of the peripheral arteries (ilio-femoral arterial

Figure 1. Multi-detector row computed tomography may give critical information in patients undergoing transcatheter aortic valve implantation. The transverse plane of the native aortic annulus (Panel A, red line) is reconstructed and detailed measurements of the aortic annulus dimensions are used for accurate valve sizing (Panels B, E, F).The morphology of the aortic valve (tricuspid or bicuspid) can be defined with accuracy (Panel C).The distance between the native annulus and the coronary ostia can be also evaluated (Panels D and G). Moreover computed tomography provides information about calcification, tortuosity and stenosis of iliofemoral arteries, identifying patients who are eligible for transfemoral access (Panels H, I, J, K). Abbreviations: D: diameter, LM: left main, RCA: right coronary artery.



system), assisting the decision for the appropriate the procedural access (transfemoral, transarterial or transapical) (Figure 1).(17)

The use of post-operative MDCT has also shed light into many procedural related complications in TAVI patients. Optimal expansion of the frames has been evaluated with MDCT and interestingly under-expanded frames may be found in 8% of patients which has been related with significant paravalvular AR and prosthesis migration.(18) The pathophysiology of paravalvular AR has also been investigated with post-operative MDCT.(17) Moreover, post-operative MDCT studies have shown that deep implantation of the frame in the left ventricular outflow tract may be responsible for new conduction disorders after TAVI.(19) In a few patients with perioperative coronary ostia occlusion successfully treated with immediate percutaneous coronary artery intervention MDCT has also revealed the possibility of direct impingement of the coronary ostia by the frame.(20)

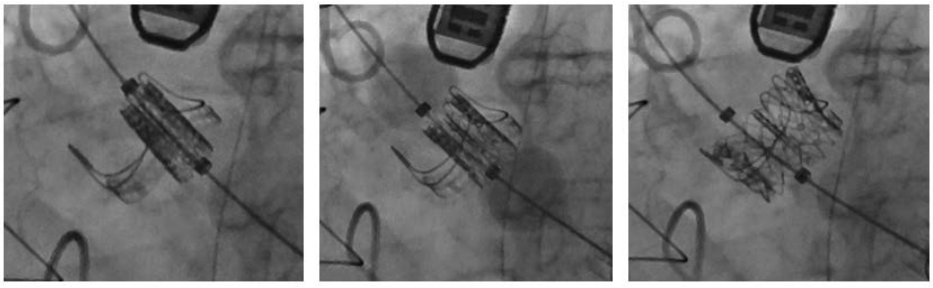
PREDICTION OF OUTCOME IN SPECIFIC POPULATIONS

In real-world clinical practice, patients with symptomatic severe aortic stenosis that do not strictly fulfil the inclusion criteria of PARTNER trial (cohort A and B) may receive a so called "off–label" treatment with TAVI. These patients are deemed at excessive surgical risk and TAVI may be a last resource treatment.

Indeed, TAVI may be a successful alternative treatment, with acceptable rate of in-hospital and long-term mortality rates, in patients with pure native aortic valve regurgitation deemed inoperable.(21) Moreover, patients with concomitant severe aortic stenosis and severe mitral regurgitation may receive TAVI treatment, although generally these cases were excluded from large randomized trials.(22) TAVI may reduce concomitant mitral regurgitation in this group. However, it remains unclear how to identify the patients that will show an improvement in mitral regurgitation after TAVI.(22)

Registries have also shown low complication rates and acceptable survival for high-risk patients with failing bioprosthesis treated with transcatheter valve-in-valve.(23) However, so far there has not been a direct comparison with a similar group of high risk patients undergoing surgical treatment (Figure 2).

Figure 2. Transcatheter aortic valve implantation may have an "off- label" use for failing bioprtosthetic valves. Successful implantation of a 23 mm Edwards SAPIEN valve in a failing 23 mm Carpentier Edwards PERIMOUNT aortic bioprosthesis.



OBJECTIVES AND OUTLINE OF THE THESIS

The objective of this thesis was to investigate the role of MDCT to predict outcomes in patients undergoing TAVI and also to focus on the outcome of specific populations undergoing this procedure.

In part I, the role of MDCT to predict the occurrence of procedural complications will be evaluated, focusing on the combination of pre- and post-procedural MDCT for the definition of the underlying mechanisms of complications such as paravalvular regurgitation (Chapter 2) or new onset rhythm conduction disturbances (Chapter 3). Addition-

ally, the deployment of the frame in relation to the coronary ostia will be systematically studied with post-operative MDCT and its implications for percutaneous coronary interventions at follow-up will be carefully addressed (Chapter 4). The combination of pre- and post-procedural MDCT images in addition to echocardiography measurements may also help us better identify the prevalence of late pericardial effusion in patients treated with TAVI (Chapter 5). Patients undergoing transfemoral TAVI do not experience pleuro-pericardial surgical trauma and they are expected to develop less frequently late pericardial effusion as compared with patients treated with transapical TAVI.

In part II the outcomes of specific populations undergoing TAVI will be studied. The predictive value of valvuloarterial impedance (ZVa) will be tested in patients undergoing TAVI (chapter 6). Ideally high baseline ZVa values would help us to identify a subgroup of patients with poor outcome, and this measurement could be included in future TAVI risk scores. Patients with more than mild mitral regurgitation represent also a special subgroup of interest (Chapter 7). There are few studies investigating predictors of mitral regurgitation improvement post-TAVI and they are based only in semiquantitative methods for grading mitral regurgitation severity. Patients with significant baseline mitral regurgitation will be followed up to 12 months after the procedure. Quantitative measurements of baseline mitral regurgitation severity will be evaluated for their ability to predict post-operative mitral regurgitation improvement. Finally, the subgroup of patients with failing bioprostheses treated with TAVI will be investigated (Chapter 8). The long-term survival of these patients will be compared with the survival of patients with similar surgical risk undergoing valvular redo surgery.

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Part I

Multi-detector row computed tomography to plan transcatheter aortic valve implantation and to evaluate the results

Chapter 2

Multidetector Row Computed Tomography Parameters Associated With Paravalvular Regurgitation After Transcatheter Aortic Valve Implantation

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Am J Cardiol 2013;112:1800-6

ABSTRACT

Background: Multidetector row computed tomography (MDCT) assessment of aortic annulus dimensions and frame position and deployment have been associated with paravalvular aortic regurgitation (PAVR) after transcatheter aortic valve implantation (TAVI). The present evaluation investigated the (pre- and post-procedure) MDCT associates of PAVR≥2+. **Methods:** In total, 123 patients referred for TAVI underwent clinical evaluation, transthoracic echocardiography and pre- and post-TAVI MDCT. Pre-TAVI MDCT measurements of the aortic annular dimensions and post-TAVI MDCT evaluation of the position and deployment of the prosthesis in the native annulus were performed. **Results:** At 1 month follow-up, PAVR≥2+ was observed in 25 (20.3%) patients. The difference between the MDCT derived maximum diameter of the aortic annulus and the nominal diameter of the implanted prosthesis (OR 1.912, p=0.002) and shallow position of the frame in the LVOT (<2mm) (OR 4.865, p=0.017) were independently related to significant PAVR. A maximum annulus diameter ≥2 mm larger than the nominal frame diameter had 72% sensitivity and 61% specificity to predict PAVR. **Conclusion:** In patients undergoing TAVI, ≥2 mm difference between maximum aortic annulus diameter and nominal prosthesis diameter, as well as depth of the frame into the LVOT <2mm are independently associated with PAVR≥2+.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established alternative for patients with severe aortic stenosis and high operative risk mortality or contraindications for surgical aortic valve replacement.(1-3) Paravalvular aortic regurgitation (PAVR) remains still as one of the main concerns of this therapy since the prognostic implications of PAVR are not negligible and data from the PARTNER cohort B trial have shown a two-fold increased mortality among patients with mild or more PAVR compared with patients showing none or trace PAVR.(4)

Determinants of PAVR are still debated. Of particular importance is the measurement of aortic valve annular dimensions with 3-dimensional imaging techniques such as multidetector row computed tomography (MDCT) since relative undersizing of the transcatheter prosthesis has been related to increased incidence of PAVR.(5-7) In addition, position and deployment of the prosthesis have been suggested as relevant underlying mechanisms of PAVR after TAVI.(7-9) However, few studies have demonstrated the relevance of post-procedural MDCT to identify the determinants of PAVR after TAVI. Accordingly, the present study aimed to identify the MDCT-derived pre- and post-procedural parameters independently associated with significant PAVR after TAVI.

METHODS

Patients with symptomatic severe aortic stenosis and high risk or contraindications for surgical aortic valve replacement were evaluated for TAVI. A heart team consisting of clinical, imaging and interventional cardiologists, cardiac surgeons and anesthesiologists agreed on the indication for TAVI following the European Society of Cardiology and the European Association of Cardio-Thoracic Surgery guidelines.(10) Prior to TAVI, all patients underwent clinical evaluation, including estimation of the operative risk based on logistic EuroSCORE, (11) comprehensive thansthoracic echocardiography (TTE) to estimate the aortic stenosis severity, MDCT to size the aortic annulus and evaluate the anatomy and dimensions of the peripheral arteries, and invasive coronary angiography to exclude significant coronary artery disease amenable to percutaneous intervention. One month after TAVI, TTE was used to assess the prosthetic valve function, whereas the deployment and position of the prosthetic valve were evaluated on MDCT. The pre- and post-procedural MDCT data on aortic root anatomy and geometry and apposition of the prosthetic valve within the native aortic annulus were related to the presence of significant PAVR after TAVI. Clinical, echocardiographic and MDCT data were prospectively collected in an electronic clinical patient file (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed. The institutional review board approved this retrospective analysis.

TAVI was performed at the hybrid operating room under general anesthesia. Fluoroscopy was the mainstay imaging technique to guide the procedure assisted by transesophageal echocardiography (iE33, Philips Medical System, Andover, MA, USA). A 23-, 26- or 29-mm Edwards Sapien and Sapien XT valve (Edwards Lifesciences, Irvine, CA) was implanted based on the dimensions of the aortic annulus. The transfemoral approach was the preferred delivery technique whereas the transapical approach was performed in patients with non-suitable peripheral artery anatomy or in patients in whom a 29-mm valve was implanted.(12) During rapid right ventricular pacing, aortic valve balloon dilatation was performed and subsequently the balloon-expandable prosthesis valve was deployed.(12) The presence of significant PAVR was evaluated with transesophageal echocardiography and re-ballooning of the prosthesis or valve-in-valve were performed as bail-out techniques to reduce aortic regurgitation severity. Patients who underwent a valve-in-valve procedure were excluded from further analysis.

A commercialy available ultrasound system (Vivid 7, E9, General Electric Horten, Norway) was used for pre- and post-TAVI TTE. The pre-procedural evaluation included the assessment of the valve morphology at the parasternal short-axis view, and the left ventricular outflow tract (LVOT) diameter was measured at the parasternal long-axis view.(13) The peak and mean transaortic pressure gradients were assessed in the apical long-axis or 5-chamber views and the aortic valve area was calculated with the continuity equation.(13) Aortic stenosis was considered severe if aortic valve area was $<1.0\ cm^2$ and/or the transaortic mean gradient was ≥40 mmHg.(14) LV end-diastolic and end-systolic volumes were calculated with the Simpson's method and LV ejection fraction was derived.(15)

In order to evaluate the presence of PAVR after TAVI, color-flow Doppler echocardiography was performed after optimization of Nyquist limit and gain settings. PAVR was evaluated on multiple echocardiographic views and conventional criteria such as the vena contracta width, the ratio of the regurgitant jet width to the LVOT diameter, pressure half-time and the proportion of the circumference of the sewing ring occupied by the regurgitant jet were used to estimate the PAVR (0 absent, 1+ trace or mild, 2+ mild-to-moderate, 3+ moderate-to-severe and 4+ severe).(16, 17) PAVR ≥2+ at the first post-operative month was considered significant.

All patients underwent pre- and post-TAVI MDCT of the aortic root using either a 64- or a 320-detector row computed tomography scanner (Aquilion64, Toshiba Medical Systems, Otawara, Japan and Aquilion ONE, Toshiba Medical Systems, Tochigi-ken, Japan). With the Acquilion 64 system, the data was acquired with a collimation of 64x0.5 mm and a gantry rotation time of 400 ms whereas the tube current was 300-400 mA and the voltage was 120 kV or 135 kV, depending on body mass index of the patients. With the Acquilion ONE system, the data was acquired with a collimation of 320x0.5 mm, gantry rotation time of 350 ms and tube current and voltage set at 400-580 mA and 100

kV, 120 kV or 135 kV (based on body mass index of the patients), respectively. Unless contraindicated, patients received beta-blockers if their heart rate was ≥70 beats per minute. All scans were performed during mid-inspiratory breath-hold and 80-90 mL of non-ionic contrast (Iomeron 400, Bracco, Milan, Italy) was injected into the antecubital vein. Subsequently, data sets were reconstructed and off-line post-processing of MDCT images was performed on dedicated workstations (Vitrea2, Vital Images, Minneapolis, Minnesota, USA).

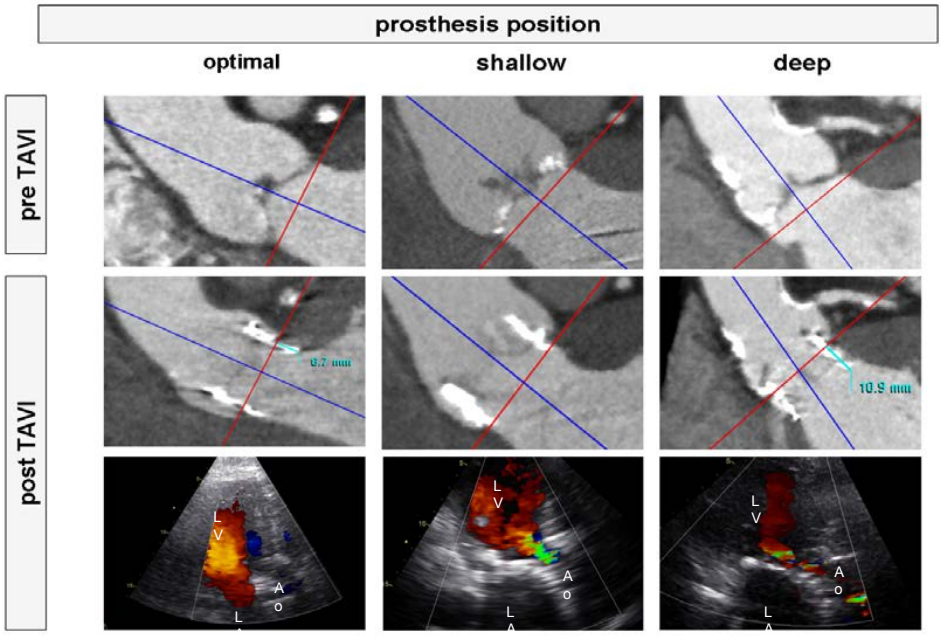
Diastolic and systolic images of the aortic root at the respective 75% and 30-40% of RR interval were selected. By aligning the three orthogonal multiplanar reformation planes, the double-oblique transversal plane that bisects the aortic annulus beneath the hinge points of the aortic cusps was obtained. At this level, the minimum and maximum aortic annulus diameters and the annulus area were measured. From the orthogonal sagittal and coronal views, the aortic annulus diameters were also measured as previously described.(18) In addition, from the non-contrast enhanced images, the calcium Agatston score of the aortic valve and landing zone was calculated. On 1-month follow-up MDCT scans, the prosthesis deployment and position in relation to aortic root were evaluated. (8) Particularly, the distance between the lower rim of the prosthesis frame in the LVOT and the native aortic annulus at the level of the left coronary cusp (LCC) was measured (Figure 1). Moreover, the distance between the upper rim of the valve frame and the right and left coronary ostia was evaluated. Additionally the prosthesis deployment was visualized at the double-oblique transverse plane of the aortic annulus. At this level, the area of the deployed prosthetic valve was assessed by planimetry and additionally the maximal and minimal diameters of the prosthetic valve frame were measured.

Following previous studies, an eccentricity index, calculated as [1-(minimum prosthesis diameter /maximum prosthesis diameter)] ≥0.1 defined a noncircular deployment of the prosthesis.(8) Moreover shallow or deep implantation of the frame were evaluated and defined as depth of the frame in the LVOT<2 mm or >8 mm from the level of the hinge point of the LCC, respectively (Figure 1).

Additionally the difference between the MDCT derived coronal and maximal diameters of the aortic annulus and the nominal diameter of the implanted prosthesis were calculated. Furthermore, the difference between the MDCT derived aortic annular area and the nominal area of the implanted prosthesis was also assessed. Among several pre- and post-TAVI MDCT parameters, the determinants of PAVR were evaluated.

All analyses were performed with a package of SPSS software version 17, (SPSS Inc., Chicago, IL, USA). Based on visual inspection of the histograms and the Kolmogorov-Smirnov tests, continuous variables were considered normally distributed and presented as mean and standard deviation or non-normally distributed and presented as median and interquartile range. Categorical variables are presented as number and frequencies. Patients were categorized according to the presence of non-significant PAVR (<2+) or

Figure 1. Examples of optimal (6.7 mm), shallow (0 mm) and deep (10.9 mm) deployment of prosthesis in the left ventricular outflow tract, leading to trivial, mild and trivial paravalvular regurgitation at 1 month follow up, respectively. Shallow deployment was considered <2 mm and deep deployment >8 mm distance from the level of the left coronary cusp in the in the left ventricular outflow tract.



significant PAVR (≥2+) at 1-month follow-up. Continuous variables were compared with the unpaired Student's t-test if normally distributed or the Mann-Whitney test otherwise. Categorical variables were also compared with the χ^2 test or Fisher's exact test, as appropriate. Receiver operating characteristic curve analyses were performed to assess the accuracy of several MDCT parameters to predict the presence of PAVR≥2+ and the cut-offs values for each variable were obtained from the highest sum of sensitivity and specificity. Binary logistic regression analysis was performed to evaluate independent determinants of PAVR≥2+ and the estimated odds ratios (OR) and the 95% confidence intervals (CI) were calculated. Variables with a $p<0.1$ in the univariate analysis were included in the multivariate model. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

A total of 123 patients (81±7 years, 49% male) with symptomatic severe aortic stenosis treated with TAVI and complete evaluation including pre- and post-TAVI MDCT were evaluated. The baseline characteristics of the patients are listed in Table 1.

Repeated balloon-dilatation of the prosthesis was performed in 15 (12.2%) patients. In 10 (66%) patients PAVR significantly reduced (<2+) after this intervention. At 1-month follow-up, all patients underwent TTE. In 30(24.4%) patients, no PAVR was observed whereas in respective 68 (55.3%), 22 (17.9%) and 3 (2.4%) patients, trivial-to-mild, mild-to-moderate and moderate-to-severe PAVR were documented. Therefore, significant PAVR≥2+ was observed in 25 (20.3%) patients. In 5 of these patients a repeat balloon dilatation was performed.

Table 1. Baseline characteristics of overall population and patients with and without significant paravalvular aortic regurgitation at follow-up

Variable	Overall (n = 123)	Paravalvular aortic regurgitation<2+ (n = 98)	Paravalvular aortic regurgitation ≥2+ (n = 25)	p-value
Age (years)	81±7	81±7	80±7	0.446
Men	60 (49%)	50(51%)	10 (40%)	0.325
Body surface area (m^2)	1.7±0.3	1.7±0.3	1.7±0.4	0.998
Hypertension	47 (38%)	38 (39%)	9 (36%)	0.799
Diabetes melitus	36 (29%)	30 (30%)	6 (24%)	0.517
Peripheral vascular disease	23 (19%)	21 (21%)	2 (8%)	0.158
Smoking	28 (22%)	23 (23%)	5 (20%)	0.796
Coronary artery disease	87 (71%)	70 (71%)	17 (68%)	0.737
New York Heart Association functional class III-IV	75 (61%)	62 (63%)	13 (52%)	0.303
Pacemaker	12 (10%)	10 (10%)	2 (8%)	1.000
Atrial fibrilation	29 (24%)	21 (21%)	8 (32%)	0.266
Medications				
Beta-blockers	71 (58%)	56(57%)	15(60%)	0.796
Diuretics	76 (62%)	59(60%)	17(68%)	0.474
Statins	74 (60%)	62(63%)	12(48%)	0.164
Calcium antagonists	36 (29%)	29(29%)	7(28%)	0.876
Logistic EuroSCORE	23.4 ±14.1	23.4±14.3	21.6±13.6	0.567
Aortic valve area (cm^2)	0.73±0.18	0.72±19	0.78±0.15	0.108
Mean transaortic valve gradient (mmHg)	42±15	42±15	39±13	0.421
Left ventricular end-systolic volume (ml)	60±40	60±40	62±39	0.771
Left ventricular end-diastolic volume (ml)	112±48	113±48	109±47	0.733

Table 1. Baseline characteristics of overall population and patients with and without significant paravalvular aortic regurgitation at follow-up (continued)

Variable	Overall (n = 123)	Paravalvular aortic regurgitation<2+ (n = 98)	Paravalvular aortic regurgitation ≥2+ (n = 25)	p-value
Left ventricular ejection fraction (%)	50±13	50±13	48±13	0.510
Transcatheter aortic valve implantation approach				0.799
Transfemoral	47 (38%)	38 (36%)	9 (32%)	
Transapical	76 (62%)	60 (64%)	16 (68%)	
Edwards SAPIEN valve, n (%)				0.088
23 mm	29 (24%)	19 (22%)	10 (40%)	
26 mm	93 (75%)	78 (76%)	15 (60%)	
29 mm	1 (1%)	1 (2%)	0 (0%)	

Patients with PAVR<2+ and patients with PAVR≥2+ had comparable Agatston aortic valve scores and similar aortic valve annular diameters and area measured at pre-procedural MDCT scans (Table 2). However, the difference between the aortic annulus diameter measured in the coronal plane and the nominal diameter of the implanted prosthesis was significantly larger in patients with PAVR≥2+, compared with patients without significant PAVR. Similarly, the difference between the maximum aortic annulus diameter measured at the double-oblique transverse cross-sectional plane and the nominal diameter of the implanted prosthesis was significantly larger in patients with PAVR≥2+ compared with patients without significant PAVR. In contrast, there were no significant differences between groups in terms of difference between aortic annular area and nominal frame area (Table 2).

Based on post-TAVI MDCT data, the percentage of eccentrically deployed valves was higher among patients with PAVR≥2+ compared with patients without significant PAVR, although this difference was not statistically significant. In terms of positioning of the transcatheter aortic valve, patients with PAVR≥2+ showed more often a shallow positioning of the frame in the LVOT (<2mm) compared to patients without significant PAVR. In contrast, a deep positioning of the frame (>8mm) in the LVOT was not significantly different between groups (Table 2).

At multivariate analysis, the difference between the MDCT derived maximum diameter of the aortic annulus and the nominal diameter of the implanted prosthesis and depth of frame in LVOT <2mm were independently associated with PAVR≥2+ at 1 month follow-up (Table 3). Receiver operating characteristic curves were performed to evaluate the accuracy of MDCT measurements to predict the occurrence of PAVR≥2+ (Figure 2).

Interestingly, implanting a transcatheter aortic valve which nominal diameter was undersized ≥2 mm relative to the maximum aortic annulus diameter measured on pre-procedural MDCT had 72% sensitivity and 61.2% specificity to predict PAVR≥2+ (Figure 2).

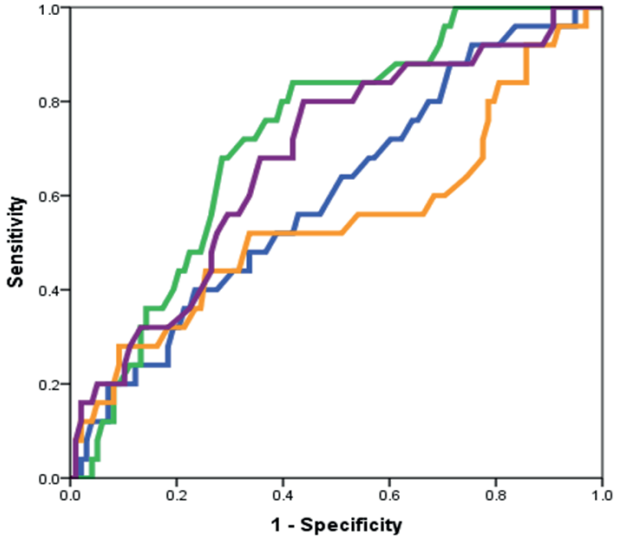
Table 2. Pre- and post-procedural multidetector row computed tomography parameters in patients with and without significant paravalvular aortic regurgitation at follow up

Variable	Paravalvular aortic regurgitation<2+ (n=98)	Paravalvular aortic regurgitation ≥2+ (n=25)	p-value
Agatston aortic valve score	2612±1394	2666± 1222	0.862
Aortic annular dimensions			
Coronal diameter (mm)	25.4± 2.1	26.0 ± 2.5	0.271
Sagittal diameter (mm)	22.8±2.0	22.6±2.2	0.551
Maximum diameter (mm)	27.1±2.4	27.9±2.3	0.092
Minimum diameter (mm)	21.1±2.0	21.2±1.9	0.868
Planimetered area (cm^2)	4.26±0.76	4.19±0.82	0.694
Difference between coronal diameter of the aortic annulus and the nominal diameter of the implanted prosthesis (mm)	0.03±1.8	1.23±1.8	0.004
Difference between maximum diameter of the aortic annulus and the nominal diameter of the implanted prosthesis (mm)	1.6±2.2	3.1±1.6	0.004
Difference between the aortic annulus area and the nominal frame area (cm^2)	−0.83±0.69	−0.65±0.67	0.237
Prosthetic valve eccentricity ≥0.1	10 (10%)	6 (24%)	0.067
Depth of frame in the left ventricular outflow tract <2 mm	7 (7%)	7 (28%)	0.003
Depth of frame in the left ventricular outflow tract >8 mm	7 (7%)	3 (12%)	0.428

Table 3. Univariate and multivariate binary logistic regression analyses

Variable	Univariate analysis		Multivariable analysis	
	Odds ratio (95% confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Agatston aortic valve score	1.000 (1.000-1.000)	0.860	….	….
Aortic annular maximum diameter	1.177(0.973-1.424)	0.094	0.718(0.498-1.035)	0.076
Difference between maximum diameter of the aortic annulus and the nominal diameter of the implanted prosthesis	1.398(1.122-1.744)	0.003	1.912(1.257-2.908)	0.002
Prosthetic valve eccentricity ≥0.1	2.779(0.900-8.577)	0.075	2.724(0.690-10.761)	0.153
Depth of frame in the left ventricular outflow tract <2 mm	5.056(1.580-16.180)	0.006	4.865(1.331-17.786)	0.017
Depth of frame in the left ventricular outflow tract >8 mm	1.773(0.424-7.411)	0.433	….	….

Figure 2. Receiver operating characteristic curve analyses of multidetector row computed tomography - related measurements of the aortic annulus to predict the occurrence of significant postoperative paravalvular aortic regurgitation.
Abbreviations: AUC= area under the curve; CI= confidence interval; Std. Error= standard error.



	AUC	Std. Error	p-value	95% CI
Maximum diameter	0.603	0.062	0.113	0.481-0.725
Difference between the maximum diameter of the aortic annulus and the nominal diameter of the implanted prosthesis	0.723	0.051	0.001	0.623-0.823
Coronal diameter	0.547	0.072	0.468	0.406-0.688
Difference between the coronal diameter of the aortic annulus and the nominal diameter of the implanted prosthesis	0.681	0.059	0.005	0.566-0.796

DISCUSSION

The present study indicates that a large difference between the maximal annulus diameter and the nominal diameter of the prosthesis, as well as a shallow position of the frame in the LVOT, are independently associated with significant PAVR after TAVI. MDCT is a valuable imaging technique to understand the underlying mechanisms of PAVR after TAVI.

Several studies have consistently shown that aortic annulus dimensions are strongly associated with PAVR after TAVI.(5-7)Therefore, accurate measurement of aortic annulus dimensions is crucial to select the most appropriate prosthesis size and optimize the outcomes of TAVI. Accumulating evidence shows that 3-dimensional imaging techniques such as MDCT are the most accurate methods to size the aortic valve annulus.(5-7) However, the golden standard measurement of the aortic annulus to select the most appropriate prosthesis size has not been established to date. Mean aortic annulus diameter

(derived from the average of the minimum and maximum diameters), area-derived diameter, coronal and sagittal diameters have been proposed to select the transcatheter valve size.(5-7) Importantly, the nominal diameter of the available transcatheter valves should be taken into consideration to estimate the grade of over- or undersizing relative to the aortic annulus once the valve is implanted. A significant oversizing of the prosthesis will minimize the risk of significant PAVR at the expense of increasing the potential risk of aortic annulus rupture whereas a significant prosthesis undersizing will increase the risk of significant PAVR and, less frequent, prosthesis migration. Jilaihawi et al demonstrated that the difference between the maximum diameter of the aortic annulus as assessed with MDCT and the nominal diameter of the implanted prosthesis had the best accuracy to predict significant PAVR after TAVI.(6) Similarly, Willson et al showed that patients with a nominal transcatheter valve area <10% larger than the cross-sectional area of the native aortic annulus (less oversized) had significantly higher incidence of PAVR as compared to patients with a difference >10% (more oversized) (19.1% vs. 0%; odds ratio 18.4, $p<0.01$).(7) Furthermore, Hayashida and coworkers demonstrated that the use of MDCT to measure the aortic valve annulus resulted in lower incidence of PAVR after TAVI as compared with 2-dimensional transesophageal echocardiography. (5)The ratio between the nominal diameter of the transcatheter valve and the mean diameter derived from the cross-sectional area of the aortic valve annulus measured with MDCT was strongly associated with the presence of significant PAVR after TAVI (hazard ratio 0.36 per each 0.1 increase; 95% confidence interval 0.17-0.77). (5) In the present study the difference between the maximum diameter of the aortic annulus assessed with MDCT and the nominal diameter of the implanted prosthesis predicted best the presence of significant PAVR after TAVI. Therefore, estimation of the degree of prosthesis oversizing seems to be an important parameter to minimize the incidence of significant PAVR. However, this parameter should be further confirmed in prospective studies.

In addition, calcification of the aortic valve has been related to the presence of significant PAVR.(19-21) However, it remains unclear the relative merits of the total amount of valve calcification or the (asymmetrical) location of calcification.(19, 20) In the present study, there were no differences in the amount of valve calcification (as quantified with the Agatston valve score) between the two groups of patients.

Few series have reported on the association between post-TAVI MDCT parameters, such as deployment and position of the transcatheter prosthesis and the presence of significant PAVR.(8, 22) Eccentricity of the deployed prosthesis and position into the LVOT (particularly depth) have been related with significant PAVR.(8, 23, 24) The prevalence of asymmetric deployed prosthesis is variable according to the different series (ranging between 2% for balloon-expandable prosthesis to 83% for self-expandable prosthesis). (22, 25) In the present study the prevalence of eccentric deployed prosthesis was 10% and it was not independently associated with the presence of significant PAVR.

Furthermore, the depth of the deployed valve in the LVOT as assessed with left ventriculography has been related to PAVR in patients treated with self-expandable prostheses.(24) Sherif et al demonstrated that the optimal position of the self-expandable prosthesis was approximately 10 mm deep into the LVOT (as measured from the annular hinge point of the non-coronary cusp).(24) A depth >10 mm may leave part of the prosthesis frame uncovered by the sealing skirt into the LVOT and subsequently the blood may regurgitate through the frame struts. In contrast, a shallow position of the prosthesis may be associated with malapposition of the frame into the annulus that leads to subsequent PAVR. In the present evaluation a shallow position of the frame was significantly associated with the presence of significant PAVR at follow-up. These results therefore confirm previous studies underscoring the relevance of accurate positioning of the prosthesis frame.

Some limitations should be acknowledged. The grading of PAVR remains challenging and although echocardiography may be the first choice imaging technique to use, many centers still grade PAVR based on angiographic scores immediately at the hybrid room.(26) Although an integrative approach was used to grade PAVR (as advocated by current recommendations),(16, 27)some of the variables were not systematically feasible (such as for example diastolic flow reversal in the descending aorta). In addition, 24% of patients had atrial fibrillation which may impact on the echocardiographic measurements. Furthermore, the present population included a majority of patients undergoing transapical TAVI. In addition, the present results are based on one commercially available transcatheter prosthesis (the Edwards Sapien and Sapien XT valves) and mainly on 23- and 26 mm valves. Therefore, the results may not be applicable to other manufacturers.

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Chapter 3

Multi-detector row computed tomography after transcatheter aortic valve implantation: insights into new onset rhythm conduction disorders

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Submitted

ABSTRACT

Background: New onset rhythm conduction disorders are frequent after transcatheter aortic valve implantation (TAVI). Multi-detector row computed tomography (MDCT) may help elucidate the pathophysiology of rhythm conduction disorders in patients treated with the Edwards SAPIEN valve. **Methods:** A total of 94 patients (age 81±7 years, men 48%) treated with TAVI with the Edwards SAPIEN valve and undergoing a pre- and post-TAVI MDCT were included. Patients with pre-existent right or left bundle branch block (LBBB) and permanent pacemakers were excluded. Position and deployment of the transcatheter frame into the aortic root was evaluated at post-TAVI MDCT. Pacemaker implantation or new onset LBBB at 1 month follow-up was the combined endpoint. **Results:** Overall, 1 pacemaker was implanted and 14 new onset LBBB were recorded. Among several tested clinical and MDCT variables, overexpansion of the transcatheter valve >15% of the native annulus area (odds ratio 5.277, 95% confidence interval 1.398-19.919, p = 0.014) and depth of frame into the left ventricular outflow tract (LVOT) (odds ratio1.401, 95% confidence interval 1.066-1.770, p = 0.010) were independently related to the need for pacemaker or new onset LBBB. **Conclusions:** Overexpansion of the transcatheter prosthesis by >15% of native aortic annulus area and implantation depth of the frame into the LVOT are independently associated with the need for pacemaker or new onset LBBB in patients undergoing TAVI with the Edwards SAPIEN valve.

INTRODUCTION

New onset persistent left bundle branch block (LBBB) after transcatheter aortic valve implantation (TAVI) has been described in 10-19% of patients receiving an Edwards SAPIEN prosthesis (Edwards Lifesciences, Irvine, CA) and in 28-57% of patients receiving a CoreValve system (Medtronic, Minneapolis, MN).(1-4) Likewise, the need for permanent pacemaker implantation is higher among recipients of the CoreValve system (23-33%) compared with recipients of the Edwards SAPIEN valve (2.5-11.5%).(3-6) Besides the different design characteristics of these two devices, which may be associated with the differences in incident new onset LBBB or pacemaker implantation, baseline QRS complex duration and deep implantation of the prosthesis into the left ventricular outflow tract (LVOT) have been consistently associated with these complications after TAVI.(2,4) Particularly, the implantation depth may vary considerably with the CoreValve system which has a longer frame than the Edwards SAPIEN valve. The series that have observed the association between implantation depth into the LVOT and the development of new onset LBBB and need for permanent pacemaker have assessed this parameter based on aortograms performed immediately after valve deployment.(2,4) The higher spatial resolution of multi-detector row computed tomography (MDCT) allows more accurate evaluation of the spatial relationships of the implanted prosthesis into the aortic root and may help elucidate the pathophysiology of the development of new onset LBBB and need for permanent pacemaker in patients undergoing TAVI. The present study evaluated the MDCT associates of new onset LBBB and need for pacemaker in patients treated with TAVI.

METHODS

Patient population

The study included 94 patients undergoing TAVI with the Edwards SAPIEN valve (Edwards SAPIEN or SAPIEN XT, Edwards Lifesciences, Irivine, CA) at the Leiden University Medical Center (Leiden, The Netherlands). Information about inclusion criteria in the TAVI registry and procedural details has been previously described in detail.(7) Patients with bioprosthetic aortic valves and valve-in-valve implantation as a bailout procedure were excluded. Unless contraindicated, patients referred for TAVI are evaluated with pre-procedural MDCT for accurate measurement of the native aortic annulus and valve sizing. One month after TAVI, a second MDCT is performed in order to define the deployment of the prosthesis in the LVOT and aortic root. Following successful TAVI procedure patients are followed-up in the outpatient clinic with scheduled visits at 1, 3, 6 and 12 months. Clinical evaluation, surface electrocardiogram (ECG) and echocardiography

are routinely performed. All clinical information on demographics, ECG, and imaging techniques are digitally stored in the departmental database (EPD vision version 8.3.3.6; Leiden, The Netherlands) and can be retrospectively analyzed. For this study, baseline clinical data in combination with pre- and post-TAVI MDCT parameters were related to the combined endpoint: need for pacemaker implantation or new onset persistent LBBB at 1 month follow-up. For this retrospective analysis, the Institutional Review Board waived the need for patient written informed consent.

ECG analysis

All ECGs were retrospectively reviewed at 3 time points: baseline (pre-TAVI), during hospitalization and at 1 month follow-up. The presence of RBBB and LBBB was diagnosed according to current recommendations.(8) Duration of the PR interval and QRS complex were automatically calculated with dedicated software (Ziemens/ Dräger, Mega Care ECG Management System, Lubeck, Germany).

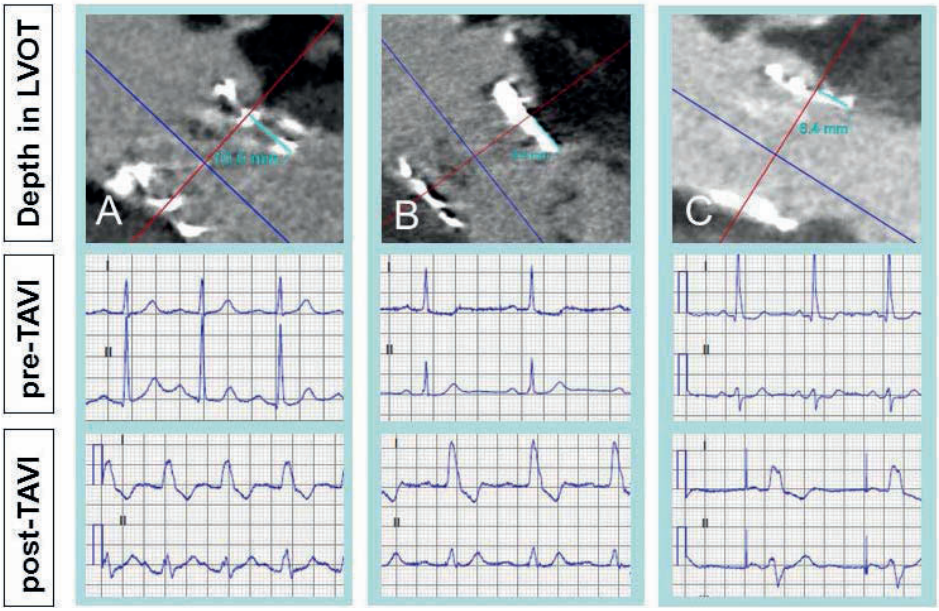
Multi-detector row computed tomography

A 64- or a 320-detector row computed tomography scanner was used for pre-operative and post-operative scanning of the patients. When the Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan) was used, data were acquired with a collimation of 64 x 0.5 mm and a gantry rotation time of 400 ms (tube current was 300-400 mA, voltage was 120 kV or 135 kV) and when the AcquilionONE system was used, data were acquired with a collimation of 320 x 0.5 mm (gantry rotation time of 350 ms, tube current and voltage set at 400-580 mA and 100 kV, 120 kV or 135 kV according to patients body mass index).

According to the acquisition protocol, patients with heart rate ≥70 beats per minute received beta-blockers unless contraindicated. A volume of 80-90 mL of non-ionic contrast (Iomeron 400, Bracco, Milan, Italy) was used according to patients' body surface area. Scans were acquired in mid-inspiratory breath-hold and data was digitally stored.

Post-processing workstations (Vitrea2, Vital Images, Minneapolis, Minnesota, USA) were used for off-line analysis of the data. In the pre-TAVI MDCT data, the Agatston score of the aortic valve annulus and the LVOT was calculated. The calcification of LVOT (sub-annular landing zone) was semiquantitatively graded (1: none, 2: mild, 3: moderate, 4: severe).(9) Accurate measurements of the aortic annulus and root dimensions were performed. Aligning the coronal, sagittal and transverse orthogonal planes across the aortic annulus, the cross sectional area, minimum and maximum diameters were measured.(10) In the post-TAVI MDCT, the expansion of the aortic valve was defined at the same level of the aortic annulus. Using the inner margins of the expanded frame as reference, the maximum and minimum diameters were measured and the effective area of expansion was planimetered. To define the depth of implantation, the distance

Figure 1. Multi-detector row computed tomography can define implantation depth of the frame in the left ventricular outflow tract. The red line illustrates the level of the native aortic annulus. The distance between the native aortic annulus and the lower rim of the frame in the left ventricular outflow tract can be measured. There was an induction of a new onset left bundle branch block in patients (A) and (B) at one month follow-up and a new pacemaker was implanted in patient (C) at the 5th postoperative day. LVOT: left ventricular outflow tract. TAVI: transcatheter aortic valve implantation.



between the rim of the frame in the LVOT and the native aortic annulus was measured (Figure 1).(10)

The ratio (effective planimetered prosthesis area - MDCT derived aortic annulus area)/MDCT derived aortic annulus area was calculated from pre- and post-TAVI MDCT measurements as a parameter of prosthesis expansion. Prosthesis overexpansion was considered significant when the area of the expanded frame was >15% larger than the native aortic annulus valve area.(9,11)

Statistical analysis

A package of SPSS software version 20, (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. Continuous variables were considered normally or not normally distributed based on visual inspection of the histograms and were presented as mean and standard deviation or median and inter-quartile range, respectively. Categorical variables were presented as number and frequencies. Patients were categorized according to the need for new pacemaker implantation or the induction of new onset LBBB (patients with combined endpoint vs. patients free of combined endpoint). Continuous variables were compared with the unpaired Student's t-test if normally distributed or

the Mann-Whitney test otherwise. Categorical variables were compared with the χ^2 test or Fisher's exact test, as indicated. Binary logistic regression analysis was used for the evaluation of the occurrence of the combined endpoint at 1 month follow-up and the estimated odds ratios and the 95% confidence intervals were calculated. Variables with a $p < 0.1$ in the univariable model were included in the multivariable analysis. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

From an initial cohort of 161 patients in whom a pre- and post-procedural MDCT was available, 21 patients with right bundle branch block (RBBB), 24 patients with LBBB and 22 patients with permanent pacemakers at baseline were excluded. Baseline clinical and echocardiographic characteristics of the remaining 94 patients (81±7 years old, 48% men) who were finally included in the current analysis are outlined in Table 1. The mean logistic Euroscore was 20.0±11.7%. Fifty-six (60%) patients had NYHA II-IV heart failure symptoms. Overall, 38 (40%) patients were treated through a transfemoral approach and the remainder 56 (60%) through a transapical approach. The size of the implanted vales was 23 mm in 28 (30%) patients, 26 mm in 62 (66%) and 29 mm in 4 (4%). In 9 (10%) patients, reballooning of the implanted prosthesis was performed to minimize paravalvular aortic regurgitation. Eighty patients were in sinus rhythm and the remaining 14 patients had atrial fibrillation. In patients in sinus rhythm, the PR interval was 179±24 ms. In the overall population, the mean QRS duration was 98±10 ms and 7 (7%) patients had left axis deviation.

Table 1. Baseline characteristics of patients

Clinical data	**n = 94**
Age (years)	81±7
Male, n (%)	45(48)
Body surface area (m^2)	1.71±0.31
Creatinine (μmol/L)	87(70-101)
Hypertension, n (%)	40(43)
Diabetes, n (%)	28(30)
Smoking, n (%)	22(23)
Coronary artery disease, n (%)	65(70)
CABG, n (%)	24(26)
NYHA functional class III-IV, n (%)	56(59)

Table 1. Baseline characteristics of patients (continued)

Clinical data	**n = 94**
Medication	
Beta-blockers	53(56)
Diuretics	55(58)
Statins	57(60)
Calcium channel blockers	29(31)
Logistic Euroscore (%)	20.0±11.7
Procedural data	
Transfemoral, n (%)	38(40)
Transapical, n (%)	56(60)
Balloon post-dilatation, n (%)	9(10)
Edwards SAPIEN valve	
23 mm, n (%)	28(30)
26 mm, n (%)	62(66)
29 mm, n (%)	4(4)
Echocardiography data	
Aortic valve area (cm/m^2)	0.72±0.19
Intra-ventricular septum thickness (cm)	1.4±0.2
Mean transaortic gradient (mmHg)	43±17
Peak transaortic gradient (mmHg)	70±25
Left ventricular ejection fraction (%)	51±12
MDCT data	
Agatston score of the aortic valve and LVOT (Hounsfield units)	2927±1643
LVOT 'landing zone' calcification (grade 1-4)	2(2-3)
Baseline ECG data	
Heart rate (beats/min)	72 ± 12
Atrial fibrillation, n (%)	14(15)
PR interval duration (ms)	179±24
QRS duration (ms)	98±10
Left axis deviation, n (%)	7(7)

ECG: electrocardiogram; CABG: coronary artery bypass grafting; LVOT: Left ventricular outflow track; MDCT: multidetector row computed tomography; NYHA: New York Heart Association

Conduction abnormalities

Compared to baseline ECG, there was a significant increase in QRS duration in the pre-discharge ECG (from 98±10 ms to 112±22 ms, $p < 0.000$) but not in PR interval (from 179 ±29 ms to 180±41 ms, $p = 0.878$). At this time point, new onset left axis deviation in the ECG was observed in 7 (7%) patients and 11 (11%) patients developed new onset RBBB. New onset LBBB developed in 15 (16%) patients pre-discharge. Moreover, 1 (1%) patient

underwent a dual-chamber pacemaker implantation 5 days after TAVI due to persistent 3rd grade atrio-ventricular block (Figure 1).

Compared to pre-discharge ECG, there were no significant changes in QRS complex or PR interval duration at 1 month follow-up (from 112±22 ms to 111±23 ms, p = 0.461 and from 180±41 ms to 179 ±36 ms, p = 0.781, respectively). In the repeat surface ECG at 1 month there were 7 (7%) patients with left axis deviation, 10 (10%) patients with RBBB and 14 (14%) patients with LBBB. New onset inhospital RBBB and LBBB resolved in 1 and 2 patients at 1 month follow-up, respectively. Moreover 1 patient developed a new onset LBBB post-discharge at 1 month follow-up. Consequently, the combined endpoint of the study at 1 month follow-up was met in 15 (16%) patients.

Post- TAVI MDCT

Post-TAVI MDCT scans showed that the deployed prosthesis was overexpanded by >15% of the native annulus area in 18 (19%) patients. Interestingly, Edwards SAPIEN valves expanded to their nominal area in only 2 patients whereas in the majority of patients frames were underexpanded. In the post-TAVI scan the mean depth of the deployed frame in the LVOT was 4.2±2.4 mm.

MDCT parameters associated with need for permanent pacemaker implantation and new onset LBBB

The study endpoint (need for permanent pacemaker implantation and/or new onset persistent LBBB) was observed in 15 (16%) patients. As shown in Table 2, the proportion of Edwards SAPIEN valves that were overexpanded by >15% of the native aortic annulus as assessed with MDCT was higher in patients who met the study endpoint compared to patients free of the combined endpoint (6 (40%) vs. 12 (15%), p = 0.025). Also the frame was implanted deeper in the LVOT of patients that required a new pacemaker or developed new LBBB compared to patients free of the combined endpoint (5.7±2.7 mm vs. 4.0±2.3 mm, p = 0.014, respectively) (Table 2). Binary logistic regression analysis showed that overexpansion of the valve by >15% of the native aortic annulus (OR 5.277, 95% CI

Table 2. Comparison between patients with new onset LBBB or need for pacemaker implantation at 1 month follow-up vs. patients free of endpoint.

	Combined endpoint (n = 15)	Free of endpoint (n = 79)	p-value
Age (years)	81±4	80±7	0.678
Male, n (%)	9(56)	37(47)	0.492
Body surface area (m^2)	1.84±0.27	1.69±0.31	0.092
Creatinine (μmol/L)	83(57-97)	88(71-102)	0.556

Table 2. Comparison between patients with new onset LBBB or need for pacemaker implantation at 1 month follow-up vs. patients free of endpoint. (continued)

	Combined endpoint (n = 15)	Free of endpoint (n = 79)	p-value
Hypertension, n (%)	9(60)	31(39)	0.136
Diabetes, n (%)	4(25)	24(30)	0.667
Smoking, n (%)	3(20)	19(24)	0.734
Coronary artery disease, n (%)	11(73)	54(68)	0.702
CABG, n (%)	5(31)	19(24)	0.648
NYHA functional class III-IV, n (%)	9(60)	47(59)	0.917
Medication			
Beta-blockers	8(47)	45(57)	0.609
Diuretics	8(53)	47(59)	0.675
Statins	10(40)	47(59)	0.602
Calcium channel blockers	6(40)	23(29)	0.403
Logistic Euroscore (%)	22.7±9.4	19.4±12.1	0.332
Transfemoral, n (%)	6(38)	32(41)	0.832
Transapical, n (%)	9(60)	47(59)	0.971
Balloon post-dilatation, n (%)	2(13)	7(8)	0.865
Edwards SAPIEN valve			
23 mm, n (%)	2(13)	26(33)	0.129
26 mm, n (%)	13(86)	49(62)	0.065
29 mm, n (%)	0(0)	4(5)	0.373
Echocardiography data			
Aortic valve area (cm/m^2)	0.76±0.16	0.71±0.19	0.324
Intra-ventricular septum thickness (cm)	1.4±0.3	1.4±0.2	0.915
Mean transaortic gradient (mmHg)	45±21	43±16	0.634
Peak transaortic gradient (mmHg)	76±33	69±24	0.339
Left ventricular ejection fraction (%)	51±12	52±12	0.818
MDCT data			
Agatston score of the aortic valve and LVOT (Hounsfield units)	3026±1765	2909±1633	0.814
LVOT 'landing zone' calcification (grade 1-4)	2(2-3)	2(2-3)	0.440
Baseline ECG data			
Heart rate (beats/min)	73±13	71±11	0.446
Atrial fibrillation, n (%)	3(19)	11(14)	0.629
PR interval duration (ms)	188±39	177±21	0.203
QRS duration (ms)	97±10	98±10	0.630
Left axis deviation, n (%)	7(46%)	0 (0%)	0.231

ECG: electrocardiogram; CABG: coronary artery bypass grafting; LVOT: Left ventricular outflow track; MDCT: multidetector row computed tomography; NYHA: New York Heart Association.

Table 3. Univariate and multivariate analysis of clinical, electrocardiogram and MDCT parameters related to new onset persistent LBBB or need for pacemaker implantation at 1 month follow-up.

Variables	Univariate		Multivariate	
	Odds Ratio (95% Confidence Interval)	p-value	Odds Ratio (95% Confidence Interval)	p-value
Age (years)	1.018 (0.938-1.104)	0.675		
Male, n (%)	1.297 (0.429-3.923)	0.645		
Creatinine (µmol/L)	0.994 (0.976-1.013)	0.548		
Diabetes, n (%)	0.833 (0.241-2.882)	0.833		
CAGB, n (%)	1.447 (0.439-4.774)	0.544		
NYHA functional class III-IV, n (%)	1.200 (0.364-3.957)	0.765		
Beta-blockers, n (%)	0.795 (0.285-2.614)	0.863		
Transfemoral, n (%)	0.979 (0.317-3.020)	0.971		
Balloon post dilatation, n (%)	1.582 (0.295-8.480)	0.592		
Aortic valve area (per cm/m^2)	4.284 (0.241-76.231)	0.322		
Intra-ventricular septum (per cm)	0.988 (0.797-1.225)	0.891		
Left ventricular ejection fraction (%)	0.995 (0.953-1.038)	0.816		
Agatston score (per 100 units)	0.999 (0.956-1.044)	0.959		
LVOT 'landing zone' calcification (grade 1-4)	0.791 (0.437-1.430)	0.437		
Overexpansion >15% of native annulus area, n (%)	3.722 (1.119-12.382)	0.032	5.277 (1.398-19.919)	**0.014**
Depth of frame in LVOT (per mm)	1.320 (1.045-1.667)	0.020	1.401 (1.083-1.811)	**0.010**
Atrial fibrillation, n (%)	1.545 (0.375-6.371)	0.547		
PR duration (per ms)	1.015 (0.992-1.040)	0.208		
QRS duration (per ms)	0.987 (0.935-1.041)	0.626		

ECG: electrocardiogram; CABG: coronary artery bypass grafting; LVOT: Left ventricular outflow tract; NYHA: New York Heart Association.

1.398-19.917, p = 0.014) and depth of frame into the LVOT (OR 1.401, 95% CI 1.083-1.811, p = 0.010) were independently associated to the study endpoint (Table 3).

DISCUSSION

The present evaluation expands on the pathophysiological determinants of new onset persistent LBBB or need for pacemaker implantation in patients treated with TAVI using the balloon-expandable Edwards SAPIEN prosthesis. With the use of MDCT post-TAVI, the present evaluation demonstrated that overexpansion of the frame by >15% of the native annulus area and deep implantation of the prosthesis into the LVOT were independently related to the presence of new onset persistent LBBB and pacemaker implantation.

Incidence of new onset LBBB and need for pacemaker implantation after TAVI with the Edwards SAPIEN valve

The incidence of new conduction abnormalities in TAVI patients varies widely across the several trials.(1-3,12-22) Pre-existent conduction abnormalities, type of implanted prosthesis and timing and duration of new conduction abnormalities (early vs. late after TAVI[2](2,5,17,18,23) and transitory versus persistent abnormalities(2,17,24)) are the main confounder factors underlying the disparate incidences. Few trials and registries have documented the incidence of new onset persistent conduction abnormalities and need for pacemaker implantation after TAVI in patients without preexistent conduction abnormalities.(1-3) The PARTNER trial and the continued access registry, including 1157 patients without preexistent conduction abnormalities or pacemaker, reported an incidence of new onset of LBBB of 10.5% before hospital discharge.(1) Urena et al reported an incidence of 30.2% in 202 patients undergoing TAVI with the Edwards SAPIEN valve.(2) Using the self-expandable CoreValve system, Testa et al reported an incidence of new onset LBBB of 27.4%.(3) However, at mid follow-up, the prevalence of persistent LBBB reduced in all series: data from the PARTNER trials and the continued access registry showed a prevalence of persistent LBBB of 7.8% and 8.5% at 30 days and 6-12 months follow-up, respectively, whereas in the series by Urena et al LBBB resolved in 37.7% and 57.3% of patients at hospital discharge and 6-12 months follow-up, respectively.(1,2) Among patients treated with the CoreValve system, Testa and colleagues reported no change in LBBB prevalence at 1 month follow-up.(3) The incidence of new onset persistent LBBB in the present study (n = 14 patients, 15%) was comparable to previous studies including patients treated with the Edwards SAPIEN valve.

The incidence of new pacemaker implantation after TAVI has been reported in 9.2% to 42% among patients treated with a CoreValve system and in 2.5% to 11.5% in patients treated with the Edwards SAPIEN valve.(12,13,17-22,25) Preexistent RBBB or LBBB have been associated with increased risk of pacemaker implantation with complete atrioventricular block and symptomatic bradycardia being the main reasons for pacemaker implantation.(4,5,18,19) In the present study, patients with preexistent conduction abnormalities were excluded which would explain the low incidence of new pacemaker implantation. Complete atrioventricular block was the indication for pacemaker implantation.

MDCT associates of new onset LBBB and need for pacemaker implantation after TAVI

Several clinical and electrophysiological parameters have been associated with increased risk of new onset LBBB and pacemaker implantation after TAVI.(1-5,23,26) Among the several studies including patients with preexistent conduction abnormalities, Bagur et al(5) identified preexistent RBBB as predictor of pacemaker implantation in patients treated with the balloon-expandable valve. Among patients without preexistent con-

duction abnormalities, data from the PARTNER trials and the continued access registry showed that prior coronary artery bypass grafting was associated with increased risk of new onset LBBB(1) while Urena et al demonstrated larger baseline QRS duration and deep implantation of balloon-expandable prosthesis into the LVOT as determinants of this endpoint.(2) A low implantation of the prosthesis frame into the LVOT was also identified by Testa and coworkers as determinant of persistent LBBB in patients treated with a self-expandable valve.(3) The implantation depth of the device has been assessed in previous studies with aortography performed during the TAVI procedure.(23) Few studies have evaluated with MDCT the position of the deployed frame into the LVOT and have correlated it with the occurrence of conduction disturbances.(24,27) Binder et al showed that the implantation depth of the Edwards SAPIEN frame was significantly lower into the LVOT in 4 patients developing new LBBB compared to patients without LBBB (5.5±2.9 mm vs.3.4±2.9 mm).(24) Similarly, Caudron et al reported a mean implantation depth of 4.1± 2.6 mm in 7 patients who developed new conduction abnormalities post-TAVI compared to 2.0±2.4 mm in patients without new onset conduction disturbances.(27) The cardiac conduction system penetrates the membranous septum from right to left, and continues its course in the LVOT, giving rise to the left bundle branch which is at the base of a triangle defined by the right and non-coronary aortic cusps. A direct compression of the valve frame on the cardiac tissue in proximity to the conduction system may be the key factor to induce conduction disorders in TAVI patients.

Oversizing of the valve may also contribute to the compression force on the cardiac tissue adjacent to the conduction system, but the significance of this parameter has been debated.(2,4,23,24,26,28) Binder et al did not observe an association between oversizing or overexpansion of the frame and the occurrence of conduction abnormalities after TAVI, however only pre-discharge ECGs were evaluated and patients with baseline conduction disorders were not excluded.(24) The current study demonstrated that overexpansion of the frame by >15% in relation to the native aortic annulus was related with new onset conduction abnormalities and that this association was independent from implantation depth. Calcification of the device landing zone in the LVOT and aortic root has been also proposed as an associate factor of need of pacemaker implantation.(29) In 67 patients without pacemaker prior to TAVI, using the CoreValve system, Latsios et al assessed semiquantitatively with pre-TAVI MDCT the amount of calcification into the device landing zone. In 32% of patients, a pacemaker was implanted prior to hospital discharge. The extent and amount of calcifications in the device landing zone were associated with increased risk of pacemaker implantation at follow-up (OR 1.06, 95% CI 1.02-1.11, $p = 0.004$).(29) However, the present study does not confirm those results. The different transcatheter valves implanted and the definition of the endpoint may have precluded us to observe similar results.

Limitations

Some limitations should be acknowledged. The study was retrospective and it was performed in a single centre. Moreover, only Edwards SAPIEN and SAPIEN XT valves were used and results may not be reproducible with other commercially available valves.

CONCLUSIONS

Overexpansion of the Edwards SAPIEN frame by >15% of the native annulus area and low implantation in the LVOT were independently related to new onset of persistent LBBB and need for pacemaker implantation.

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None.

Conflict of interest statement

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Chapter 4

Position of Edwards SAPIEN transcatheter valve in the aortic root in relation with the coronary ostia: implications for percutaneous coronary interventions

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Submitted

ABSTRACT

Objectives: To determine the implications of stable coverage of the coronary ostia by the Edwards SAPIEN valve frame in terms of myocardial ischemia and subsequent percutaneous coronary intervention (PCI), following transcatheter aortic valve implantation (TAVI). **Background:** Edwards SAPIEN frame is frequently deployed relatively higher than recommended and may overlap the coronary ostia. **Methods:** A total of 142 patients (age 81±7 years, male 49%) treated with Edwards SAPIEN valve and with multi-detector row computed tomography at 1 month follow-up were evaluated. The position of the frame in relation to the coronary ostia was assessed. Levels of troponin T were measured 12-24 hours after TAVI. PCI events at follow-up were recorded. **Results:** The left coronary ostium was fully covered in 3 (2.1%) patients and the right coronary ostium in 11 (7.7%). There were no differences in troponin T levels between patients with fully covered ostia vs. patients with partly or non-covered ostia (0.24 (0.13-0.50) μg/L vs. 0.35 (0.15-0.55) μg/L, respectively; p = 0.377). At 30±15 months follow up, 10(7%) patients underwent successful PCI. Rate of subsequent PCI was similar between patients with any covered ostium and patients with non-covered ostia (4 (7.8%) vs. 6 (6.5%), p = 0.780, respectively). **Conclusions:** Full overlap of the coronary ostia by Edwards SAPIEN frame is infrequent and in most cases is not related with post-operative troponin T elevation and does not limit subsequent PCI.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an alternative treatment for patients with severe aortic stenosis who are deemed non-operable or have a very high-risk for conventional cardiac surgery.(1,2) Accurate deployment of the device is crucial to avoid complications. Very low implantation of the device has been associated with paravalvular regurgitation, mitral valve dysfunction, conduction abnormalities, and less frequent with device migration into the left ventricle. (3,4) In contrast, high position of the device into the aortic root has also been associated with paravalvular regurgitation, coronary ostia obstruction and valve migration.(5,6) The recommended position of the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA), with 50% below and 50% above the native leaflet insertion, is not always achieved.(7) An asymmetrical, operator-independent upward movement of the frame during the last steps of implantation may take place and lead to a higher final position of the device, reaching the coronary ostia. (7) While acute occlusion of the coronary ostia is a very rare complication with a reported incidence between 0.6% and 1.1% (8,9), the prosthetic frame may reach and exceed the coronary ostia without limiting the blood flow in more than 10% of patients.(5,10,11) The implications of a stable coverage of the coronary ostia by the frame remain unexplored. The permeable struts of the frame permit normal blood flow through the coronary ostia and therefore, acute ischemic events may be avoided. However, at long term follow-up, the implications of this position for subsequent percutaneous coronary interventions (PCI) have not been described. Accordingly, the present evaluation aimed at reporting the prevalence of high position of the Edwards SAPIEN frame in relation to the coronary ostia and the clinical implications of stable coronary ostia coverage by the prosthetic frame in terms of post-procedural acute ischemic events and influence on the feasibility of PCI at long-term follow-up.

MATERIALS AND METHODS

Patients

From an ongoing registry of 261 patients undergoing TAVI in our center, a total of 142 patients who underwent multi-detector row computed tomography (MDCT) after successful TAVI with Edwards SAPIEN prostheses were evaluated. Demographic and clinical data, including symptoms, associated comorbidities and medication, were collected prior to TAVI. According to the institutional protocol, patients underwent post-procedural MDCT evaluation of transcatheter valve position and deployment within the aortic root at 1 month follow-up, unless contraindications (renal dysfunction, uncontrolled atrial arrhythmias and contraindications for beta-blockers).(5)

Based on post-operative MDCT images, the distance of the prosthetic frame in relation to the coronary ostia was measured and the prevalence of complete overlap between the prosthetic frame and the coronary ostia was assessed. In addition, the need of invasive coronary angiography and PCI at long term follow up was recorded.

Clinical and imaging data were prospectively collected in the departmental Cardiology Information System (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed. The institutional review board approved the retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

Echocardiography

The severity of aortic stenosis was confirmed with transthoracic echocardiography prior to TAVI. The aortic valve morphology (tricuspid/bicuspid) was assessed at the parasternal short-axis view and peak and mean transaortic gradients were measured in the apical long-axis view. (12) The aortic valve area was calculated with the continuity equation. (12) An aortic valve area <1.0 cm^2 and/or a mean gradient ≥40 mmHg defined severe aortic stenosis. (13) Left ventricular (LV) end-diastolic and end-systolic volumes were measured according to the Simpson's method and LV ejection fraction (LVEF) was derived. (12)

TAVI procedure

All patients underwent coronary angiography before the procedure and significant coronary artery lesions amenable to PCI were treated mainly with bare-metal stents. TAVI was performed under general anesthesia with fluoroscopy and transesophageal echocardiography guidance.(14,15) A transfemoral approach was performed in patients with appropriate ilio-femoral arterial tree anatomy as defined in pre-operative MDCT. Otherwise, TAVI was performed via a transapical approach. Aortic valve balloon dilatation was performed under rapid right ventricular pacing and subsequently, a 23-, 26- or 29-mm Edwards SAPIEN or SAPIEN XT valve was implanted also under rapid right ventricular pacing. The results were evaluated with supra-aortic angiography and transesophageal echocardiography.

Assessment of myocardial injury after TAVI

Circulating levels of troponin T were measured at 6-hour intervals within 48 hours after TAVI. The peak release of troponin T was recorded. Myocardial injury was defined as troponin T circulating levels >0.5 μg/L (>10 times the 99^{th} percentile of upper reference limit).(16)

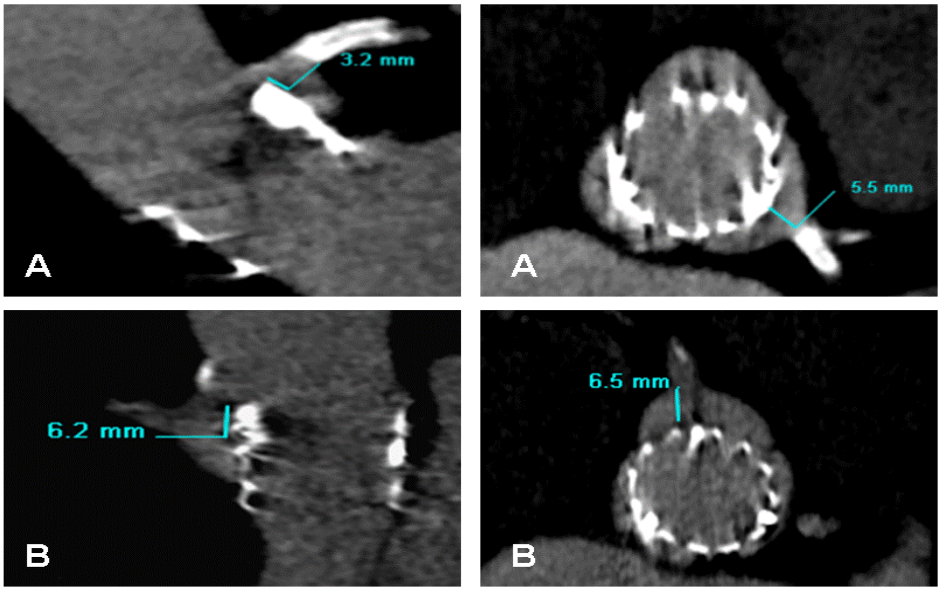
Post-operative MDCT data acquisition and analysis

Post-operative MDCT scans were performed either with a 64-(Aquilion64, Toshiba Medical Systems, Otawara, Japan) or a 320-MDCT scanner (Toshiba Medical Systems,

Tochigi-ken, Japan). For the Acquilion 64 system (collimation 64 x 0.5 mm, rotation time of 400 ms, tube current 300-400 mA, voltage 120 kV or 135 kV depending on body mass index) an ECG-gated acquisition was performed and the reconstruction of data was made at 75-85% of cardiac cycle for diastole and 30-35% for systole. With the Acquilion ONE system (collimation 320 x 0.5 mm, rotation time 350 ms, tube current 400-580 mA, voltage 100 kV, 120 kV or 135 kV according to body mass index) the entire cycle could be scanned prospectively, applying maximal tube current at 75% (for heart rate <60 beats per minute) or 65-85% (for heart rate ≥60 beats per minute) of the RR interval. Data acquisition was obtained in mid-inspiratory breath-hold. A volume of 80-90 mL of non-ionic contrast (Iomeron 400, Bracco, Milan, Italy) was administered, depending on renal function, scan time, and body weight. A heart rate <70 beats per minute was favored and achieved with beta-blockers if there was no contradiction. Post-processing analysis of MDCT images was performed on dedicated workstations (Vitrea2, Vital Images, Minneapolis, Minnesota, USA).

Using the 3 orthogonal multi-planar reconstruction planes, the spatial relation between the coronary ostia and the upper rim of the prosthetic frame was evaluated. The coronal plane was oriented to obtain a clear view of the left coronary ostium whereas

Figure 1. A: From the coronal plane the image was oriented to a point where a clear view of the left main was obtained. At this level the depth of the frame in the left ostium was measured (3.2 mm). At the same time the axial distance of the frame from the left main could be assessed (5.5 mm). B: From the sagital plane a clear image of the right coronary artery was obtained. The depth of the frame in the right coronary artery (6.2 mm) was measured and also the axial distance of the frame from the right coronary artery (6.5 mm) could be assessed.



the right coronary ostium was visualized in a sagittal view. In the coronal plane, the distance from the upper rim of the frame to the left coronary ostium was measured in all cases where the frame was reaching or exceeding the ostium (Figure 1A). In addition, the axial distance between the frame and the left ostium was measured in all cases where the frame was covering the ostium (Figure 1A). Similarly, the distance from the upper rim of the frame to the right coronary ostium was measured in the sagittal plane and the axial distance was assessed for frames exceeding the right coronary ostium (Figure 1B).

Follow-up

The occurrence of PCI after TAVI was analyzed retrospectively. The clinical indication for each procedure was defined. Specifically, all cases where PCI was performed through an ostium that was partly or fully covered were recorded.

Statistical analysis

A package of SPSS software version 20, (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Continuous variables were presented as mean and standard deviation if normally distributed or as median and interquartile range otherwise. Categorical variables were presented as number and frequencies. Patients were categorized according to the position of the prosthetic frame in relation to the coronary ostia (frame exceeding the ostia or not). Continuous variables were compared with the unpaired Student's t-test if they were normally distributed or with the Mann-Whitney test otherwise. A p-value<0.05 was considered statistically significant.

RESULTS

In the overall population of 261 patients, there were 2 (0.7%) acute coronary artery fatal occlusions: one patient undergoing transcatheter valve-in-valve implantation in a degenerated 25-mm Freestyle bioprosthesis (Medtronic, MN) in whom the degenerated prosthetic leaflets occluded the left main coronary ostia and one patient undergoing TAVI in a native valve in whom the native calcified leaflet occluded a low coronary ostium (11.2 mm from the aortic annulus). Among 142 patients (age 81±7 years, male 49%) with available post-TAVI MDCT, there were no cases of acute coronary ostia occlusion. Table 1 summarizes the clinical and echocardiographic characteristics of this population.

The mean logistic EuroSCORE was 22.8±13.8%. In 51(36%) patients, the transfemoral approach was feasible whereas in the remaining 91 (64%) patients, TAVI was performed through the transapical approach. A 23-mm valve was implanted in 38 (27%) patients, a 26-mm valve in 99 (70%) and a 29-mm valve in 5 (3%) patient. Six (4%) patients with degenerated aortic valve xenografts underwent valve-in-valve TAVI procedures. Moder-

Table 1. Baseline characteristics of patients

	N = 142
Age (years)	81±7
Male, n (%)	70 (49%)
Creatinine (μmol/L)	99±57
Hypertension, n (%)	55 (39%)
Hypercholesterolemia, n (%)	63 (44%)
Diabetes, n (%)	41 (29%)
Peripheral vascular disease, n (%)	31 (22%)
Smoking, n (%)	35 (25%)
Coronary artery disease, n (%)	99 (70%)
Logistic EuroSCORE	22.8±13.8
NYHA functional class III-IV, n (%)	83 (58%)
Pacemaker, n (%)	13 (9%)
Atrial fibrilation, n (%)	34 (24%)
Medications, n (%)	
Beta-blockers	82 (58%)
Diuretics	89 (63%)
Calcium-antagonists	42 (30%)
ACE-inhibitors / ARB-II	81 (57%)
Transfemoral / Transapical TAVI, n (%)	51 (36%) / 91 (64%)
Edwards SAPIEN XT valve	57 (40%)
Aortic valve area (cm^2)	0.7±0.2
Mean transaortic gradient (mmHg)	42±17
Max transaortic gradient (mmHg)	64±24
Left ventricular ejection fraction (%)	51±13

ACE, Angiotensin converting enzyme; ARB II, angiotensin II receptor blocker; NYHA, New York Heart Association; TAVI: transcatheter aortic valve implantation

ate to severe aortic regurgitation was treated with re-ballooning in 15 (11%) patients and in 1 patient a valve-in-valve bailout procedure was necessary.

Prevalence of coronary ostia covering by the transcatheter prosthetic frame

The frame exceeded by 1 mm the caudal rim of the left coronary ostium in 48(33.6%) patients and the right coronary ostium in 60(42.3%).The left coronary ostium was fully covered in 3 (2.1%) patients and the right coronary ostium was fully covered in 11 (7.7%) patients. In 3 (2.1%) patients, the frame was covering both ostia (Table 2).

Frames that were fully covering the coronary ostia had a mean axial distance of 3.9 (2.5-6.5) mm from the coronary ostia. Similarly, prostheses with incomplete overlap of the coronary ostia had an axial distance 3.9 mm (0-8) mm to the ostia. Table 3 summarizes the characteristics of patients with full overlap between the transcatheter valve and the coronary ostia.

Table 2. Relation of the prosthetic frame with coronary ostia

	Left coronary ostium	Right coronary ostium	Both coronary ostia	Any coronary ostia
>1 mm overlap	48 (33.6%)	60 (42.3%)	36 (25.4%)	72 (50.7%)
>3 mm overlap	31 (21.8%)	42 (29.6%)	22 (15.5%)	51 (35.9%)
Full overlap	3 (2.1%)	11 (7.7%)	3 (2.1%)	11 (7.7%)

Table 3. MDCT data of patients in whom the device frame fully overlapped the left or right coronary ostia. Ostium height is the distance between the aortic annulus and the top wall of the ostium.

Patient number	Coronary ostium covered	LCO height (mm)	RCO height (mm)	Prosthesis size	Access	Post-operative troponin T (µg/L)	Post-operative ECG changes	PCI at follow-up
1	Right	15.60	16.80	26	TF	0.02	-	-
2	Right	16.40	16.20	26	TA	0.35	-	-
3	Right	17.90	18.80	26	TA	0.24	-	-
4	Right	20.40	17.00	23	TA	0.38	-	-
5	Right	18.90	20.20	26	TF	0.04	-	-
6	Right	18.30	18.10	26	TA	0.77	-	-
7	Right	17.70	16.90	26	TF	0.13	-	-
8	Right	16.80	16.30	26	TA	0.50	-	-
9	Both	15.00	15.90	26	TA	0.51	T wave inversion I, aVL	-
10	Both	17.5	18	26	TA	0.22	T wave inversion I, V6	-
11	Both	16.50	16.40	26	TF	0.15	-	LAD,RCA

Data are expressed as number, ECG, electrocardiogram; LAD, left anterior descending artery; LCO, left coronary ostium; MDCT, multi-detector row computed tomography; PCI, percutaneous coronary intervention; RCA, right coronary artery; RCO, right coronary ostium; TA, transapical; TF, transfemoral

Acute troponin T release

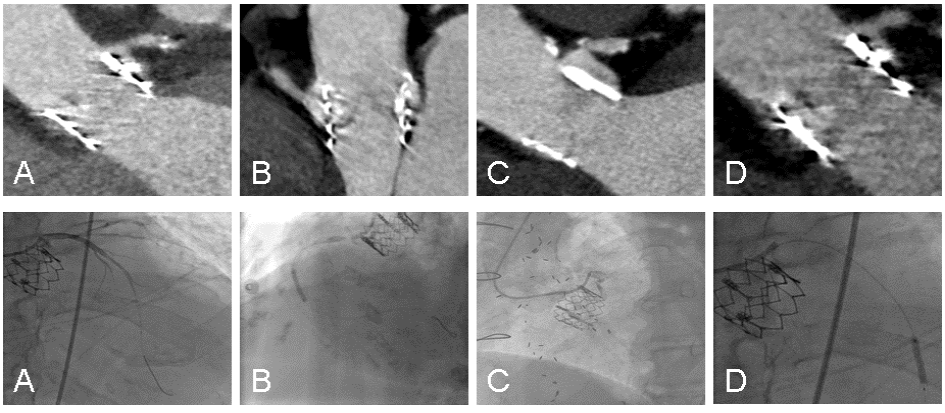
The median peak troponin T value after TAVI was 0.35 (0.15-0.55) µg/L. Overall 40 (28.1%) patients had post-operative myocardial injury (troponin T > 0.5 µg/L). There was no significant difference in post-operative troponin T levels between patients with full overlap between the transcatheter valve frame and the coronary ostia and patients with partly overlapped or non-covered coronary ostia (0.24 (0.13-0.50) µg/L vs. 0.35 (0.15-0.55) µg/L, respectively; p = 0.377). Also there was no difference in post-operative troponin T release for patients with any ostia covered >3 mm by the frame vs. non covered or covered by ≤3 mm (0.35 (0.15-0.62) µg/L vs. 0.35 (0.15-0.54) µg/L, p = 0.876). Patients with >3 mm but not fully overlapped ostia and patients with no overlapped ostia had comparable troponin T levels (0.35 (0.16-0.64) µg/L vs. 0.35 (0.14 vs. 0.45) µg/L, p = 0.965 respectively).Of note, troponin T elevation was significantly higher in patients treated through transapical as compared with transfemoral approach (0.54 (0.31-0.65) µg/L vs. 0.11 (0.05-0.18) µg/L, p < 0.000, respectively). There were no differences in troponin T levels between patients

with creatinine >90 μmol compared to those with ≤90 μmol/L (0.45 (0.14-0.62) μg/L vs. 0.39 (0.15-0.51) μg/L, p = 0.154, respectively).

Percutaneous coronary intervention at follow-up

During a mean follow up of 30±15 months, 10 (7%) patients underwent PCI. The reason for intervention was angina in 7 (4.9%) patients, progressive dyspnoea in 2 (1.4%) patients and acute coronary syndrome in 1 patient (0.7%). The median time to PCI was 13 (8-18) months. Of note, the rate of new PCI did not differ in patients full overlap between the frame and the coronary ostia and patients with partly overlapped or non-covered coronary ostia (1 (10%) vs. 9 (6%), p = 0.566, respectively) and patients with any ostium covered by >3 mm vs. patients with non-covered or covered by ≤3 mm ostia (4 (7.8%) vs. 6 (6.5%), p = 0.780, respectively).The rate of new PCI was also similar in patients with >3 mm but not fully overlapped ostia compared to patients with no overlapped ostia (3 (7.5%) vs.6 (6.5%), p = 0.556 respectively). Overall 13 drug-eluting and 1 bare-metal stents were implanted in the left anterior descending artery (7 patients), right coronary artery (3 patients) and vein grafts anastomosed to the circumflex coronary artery (4 patients). Four PCIs were performed though a partly covered or fully covered coronary ostium. Specifically, one patient underwent PCI in a fully covered left ostium (axial plane distance 3.9 mm) and a fully covered right coronary ostium (axial plane distance 5.7 mm) (Table 3) (Figure 2A, B). In the two remaining patients, PCI was performed through a coronary ostium which was partly covered by 6 mm (axial plane distance 4.6 mm) (Figure 2C) and through a left coronary ostium impeded by 4.2 mm (axial distance 3.6 mm) (Figure 2D), respectively. All procedures were successful and without major complications.

Figure 2. Percutaneous coronary interventions in ostia that are covered by the valve frame. A. Left ostium fully covered by 8 mm (axial plane distance 3.9 mm).B. Right ostium fully covered by 8.5 mm (axial plane distance 5.7 mm) in the same patient. C. Left ostium covered by 6 mm (axial plane distance 4.6 mm). D. Left ostium covered by 4.2 mm (axial plane distance 3.6 mm).



DISCUSSION

The present evaluation demonstrates that the frame of current balloon expandable valves (Edwards SAPIEN and SAPIEN XT) is frequently positioned below the coronary ostia and seldom exceeds their height. A position of the frame exceeding the coronary ostia did not increase the incidence of acute myocardial injury, neither did it hamper late PCI.

Position of the balloon-expandable prosthesis during TAVI

Accurate positioning of the transcatheter aortic valve into the aortic root is crucial to ensure proper function of the valve and minimize several complications such as device migration, paravalvular regurgitation or coronary ostia occlusion. The latter can occur during device deployment when a relatively long or bulky calcified native aortic cusp is pushed towards the coronary ostia or due to inappropriate high position of the device and the sealing cuff, for example.(17,19) This uncommon complication occurs immediately after device deployment and early diagnosis is essential for prompt and successful treatment.(19) However, a position of the balloon-expandable valve overlapping the coronary ostia without major clinical implications has been more frequently described.(5,10,11) Manufacturer's recommendations propose a 50% above and 50% below the aortic valve annulus as the ideal position for Edwards SAPIEN and SAPIEN XT valves. However, this position is not frequently achieved. In the evaluation of TAVI results with MDCT, Caudron et al demonstrated that the balloon-expandable prosthesis overlapped the left coronary ostium in 22 (71%) patients whereas the right coronary ostium was rarely covered by the device (9 [29%]).(11) The mean overlap between device and left and right coronary ostia were 2.5±2.7 mm and −0.7±3.5 mm, respectively. Fatal coronary occlusion was not described in any patient. However, the number of patients in whom the device completely exceeded the coronary ostia was not reported. Furthermore, Tamborini et al using 3-dimensional transthoracic echocardiography reported that in 16 of 110 (14.5%) patients undergoing TAVI with balloon-expandable prosthesis, the upper rim of the device reached or exceeded the left coronary ostium.(10) In these patients, the left coronary ostium height ranged between 9.3 mm and 15.6 mm. In our series, 11 of 142 (7.7%) patients showed full overlap between the prosthesis frame and the coronary ostia (Table 3). In the current study, the distance between the aortic annulus and the top wall of the left coronary ostium was 19.2 ± 2.6 mm and the right coronary ostium 19.8± 2.8 mm respectively. In another recent study Dvir and co-workers reported the final position of the SAPIEN Edwards and SAPIEN XT valves in 68 patients undergoing TAVI (7). In the majority of the patients (91.2%) the final position of the prosthesis frame was higher than recommended and <40% of the device height was placed below the aortic valve annulus. During rapid pacing, an operator-independent upward movement of the device toward the aorta was reported resulting in a higher positioning of the frame.(7)

Interestingly, the described upward movement was asymmetrical with the lower part of the device showing a larger upward displacement than the upper part of the frame (3.2±1.4 mm vs. 0.75±1.5 mm, respectively) and resulting in a shortening of the frame. The relatively stable position of the upper part of the frame may reduce the risk of coronary ostia occlusion. The authors however, did not describe the position of the prosthesis frame in relation to the coronary ostia. The current study is the first to evaluate systematically and in detail the coverage of the ostia by the valve frame with MDCT in a large population of patients undergoing TAVI. The inclusion of a larger number of patients in combination with higher spatial resolution of MDCT may account for discrepancies with previous studies.(5,10,11) The higher rate of transapical TAVI implantation in our study may be attributed to routine use of preoperative MDCT for the definition of iliofemoral artery anomalies (tortuosity, calcification) which precluded transfemoral access.

Implications of full overlap between the device and coronary artery ostia

So far there have been reports of catastrophic events following occlusion of the coronary ostia after TAVI.(8,9,18,19) However until now, the induction of paucisymptomatic ischemia has not been investigated. In our series, full overlap or covering of the ostia by >3 mm by the frame was not associated with higher risk of acute myocardial ischemia or release of post-operative troponin T compared with patients without significant overlap. The blood flow through the permeable struts of the frame may be satisfactory in most cases. Elderly patients undergoing TAVI have increased prevalence of coronary artery disease which may affect long-term mortality.(21) Although a strategy of preoperative PCI for significant coronary lesions was adopted, patients experienced late acute coronary events, angina and dyspnoea. Interestingly, in our series 7% of patients underwent PCI at 2 years follow up. So far, in most reported cases with acute occlusion of the coronary ostia during TAVI, an immediate PCI was feasible through the struts of the frame.(9,18,19) The current study confirms that late PCI through covered ostia is also feasible.

Limitations

Some limitations should be acknowledged. Only patients treated with Edwards SAPIEN valve were included and the percentage of transapical TAVI is relatively higher than other series. Moreover, the number of patients with covered ostia that underwent late PCI is small. In addition, functional tests to evaluate the presence of inducible myocardial ischemia were not systematically performed at follow-up. This is a single center experience, and the results may not be generalized to other centers with higher rates of transfemoral access or different implantation techniques. Furthermore, the low number of acute fatal occlusions of the coronary ostia precluded us to investigate predictors of this complication. However, a low take-off of the left main coronary ostia observed in one patient is one of the risk factors described by previous studies. (20)

CONCLUSIONS

Deployment of Edwards SAPIEN valve above the level of coronary ostia is not frequent and a full overlap of the ostia by the Edwards SAPIEN frame is unusual. This relative high position of the transcatheter valve frame is not associated with increased risk of acute myocardial ischemia. In addition, at long-term follow-up, PCI procedures after TAVI are feasible, even for cases where the Edwards SAPIEN valve frame is covering the ostia.

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Chapter 5

Pericardial effusion following transcatheter aortic valve implantation: echocardiography and multi-detector row computed tomography evaluation

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Submitted

ABSTRACT

Background: Although pericardial effusion (PE) early after transcatheter aortic valve implantation (TAVI) has been reported in few registries, late PE at follow-up remains unexplored. Particularly, after transapical TAVI, diagnosis of PE with transthoracic echocardiography (TTE) may be challenging. The present evaluation assessed the incidence of PE early after TAVI and at 1 month follow-up using TTE and multi-detector computed tomography (MDCT). The agreement between TTE and MDCT to diagnose the presence and severity of PE at 1 month follow-up was evaluated. **Methods:** Overall 293 patients undergoing TAVI were included. Pre-discharge TTE was performed in all patients. At 1 month, repeat TTE was performed in 234 patients and additional MDCT evaluation in 143 patients. **Results:** Pre-discharge small and moderate PE was observed in 74.1% and 4.1% of patients, respectively, whereas significant PE was diagnosed in 8 (2.7%) patients without differences between procedural access: 1.6% vs. 3.6% for transfemoral and transapical respectively, $p = 0.474$. At 1 month new-onset moderate PE was noted in 6 (2.5%) patients all of who underwent transapical TAVI. MDCT and TTE disagreed on the grade of PE in 38 patients. Importantly, 1 patient with small PE on TTE was considered having moderate PE and 2 patients with small and moderate PE were considered having large PE. Also, 2 patients with moderate PE on echocardiography were considered small PE on MDCT.**Conclusions:** Significant PE early after TAVI is infrequent. The prevalence of small and moderate PE remains stable at 1 month follow-up. MDCT refines the diagnosis of significant PE.

INTRODUCTION

The incidence of clinically significant pericardial effusion (PE) following cardiac surgery ranges between 1-29%.(1-3) This wide variability may be related to the study design (prospective series including patients referred for pericardiocentesis versus retrospective unselected series), different definitions of clinically relevant PE (from moderate PE to cardiac tamponade) and timing and methodology of diagnosis (early after surgery [<7 days] or late [≥7 days]). The factors associated with early and late PE are different: while anticoagulation exceeding therapeutic levels is associated with early PE, post-pericardiotomy syndrome is the main cause of late PE.(2,3) Transcatheter aortic valve implantation (TAVI) is a safe and feasible alternative for patients with symptomatic severe aortic stenosis and high operative risk or contraindications for surgery. Data on the incidence of significant PE and cardiac tamponade among patients undergoing TAVI are scarce: Lange et al(4) reported an incidence of 13% while in the Pilot European Sentinel TAVI registry, cardiac tamponade was observed in 2.4% of patients and the incidence was significantly higher among patients undergoing non-transfemoral TAVI compared to transfemoral TAVI (3.8% versus 2.7%, respectively, $p = 0.001$).(5) However, it remains unknown whether significant PE may develop late at follow-up. In addition, in patients undergoing transapical TAVI, echocardiographic diagnosis of significant PE may be challenging.

Multi-detector row computed tomography (MDCT) provides better spatial resolution than echocardiography for the diagnosis of early and late complications of TAVI, including significant PE. Although MDCT does not currently provide information on hemodynamics to evaluate the presence of cardiac tamponade, it may provide a more accurate quantification and localization of the PE and indirect signs of tamponade.(6-8) The aim of the current study was to evaluate the incidence and prevalence of PE as assessed with echocardiography early (in-hospital) and late (1 month) after TAVI. The agreement between MDCT and echocardiography for the detection of PE at 1 month follow-up after TAVI was also evaluated.

METHODS

From an ongoing registry of patients with symptomatic severe aortic stenosis undergoing TAVI at the Leiden University Medical Center, 293 patients with uneventful TAVI and with pre-discharge echocardiographic follow-up were included. After successful TAVI, clinical and echocardiographic follow-up were routinely performed at 1, 3, 6 and 12 months. According to the institutional protocol, at 1 month follow-up a repeat MDCT was performed unless contraindicated, to evaluate the position of the expanded pros-

thesis in the native aortic valve.(9) Demographic, clinical, echocardiography and MDCT information were digitally stored (EPD vision version 8.3.3.6; Leiden, The Netherlands) and were retrospectively analysed. Presence and severity of PE was assessed with echocardiography before hospital discharge and at 1 month follow-up. In addition, among patients with 1-month echocardiography and MDCT follow-up, the agreement between these two imaging techniques to diagnose PE was assessed. The institutional review board approved the study and waived the need for patient written informed consent for retrospective analysis of clinically acquired data.

TAVI procedure

Transcatheter aortic valve implantation procedures were performed in the hybrid room under general anaesthesia and were guided by fluoroscopy and transesophageal echocardiography (iE33, Philips Medical System, Andover, MA, USA). The CoreValve system (Medtronic Inc., Minneapolis, MN) was implanted using a transfemoral access while the Edward SAPIEN prostheses (Edwards Lifesciences, Inc., Irvine, CA) were implanted via a transfemoral access or a transapical access. Implantation technique for each device has been previously described.(10,11) Immediately after prosthesis deployment, the valve hemodynamics and presence of paravalvular regurgitation were assessed with transesophageal echocardiography. The presence of PE was also evaluated at the end of the procedure.

Echocardiography

Transthoracic echocardiography was performed with commercially available ultrasound systems (Vivid 7, E9, and S6, General Electric, Horten, Norway) equipped with M5S and M4S phased array probes. Cardiac chamber quantification was performed as recommended.(12) Left ventricular (LV) end-diastolic and LV end-systolic volumes were calculated using the Simpson's method and LV ejection fraction was derived.(12) The morphology of the aortic valve (bicuspid or tricuspid) was examined at the parasternal short-axis view. Peak and mean gradients of the aortic valve were measured at the apical long-axis or 5-chamber views. The LV outflow tract diameter was measured in a zoomed view of the parasternal long-axis view. The aortic valve area (AVA) was derived with the continuity equation. The presence of PE was assessed following current recommendations.(8) From M-mode recordings of the parasternal long-axis view, the presence of a free-echo space between the epicardium and the parietal pericardium in systole and diastole indicates >50 mL effusion. An end-diastolic space between the epicardium and the parietal pericardium of <10 mm, between 10-19 mm and ≥20 mm defined small, moderate and large PE, respectively.(13) In addition, the location and distribution of the PE was also assessed from 2-dimensional data. Furthermore, the presence of chamber collapse during diastole on 2-dimensional echocardiography, >30% respiratory flow

variation of the transmitral E-wave on pulsed wave Doppler recordings together with inferior vena cava dilatation or blunting or reversal of diastolic hepatic vein flow during expiration, were echocardiographic criteria of cardiac tamponade.(8)

Multi-detector row computed tomography

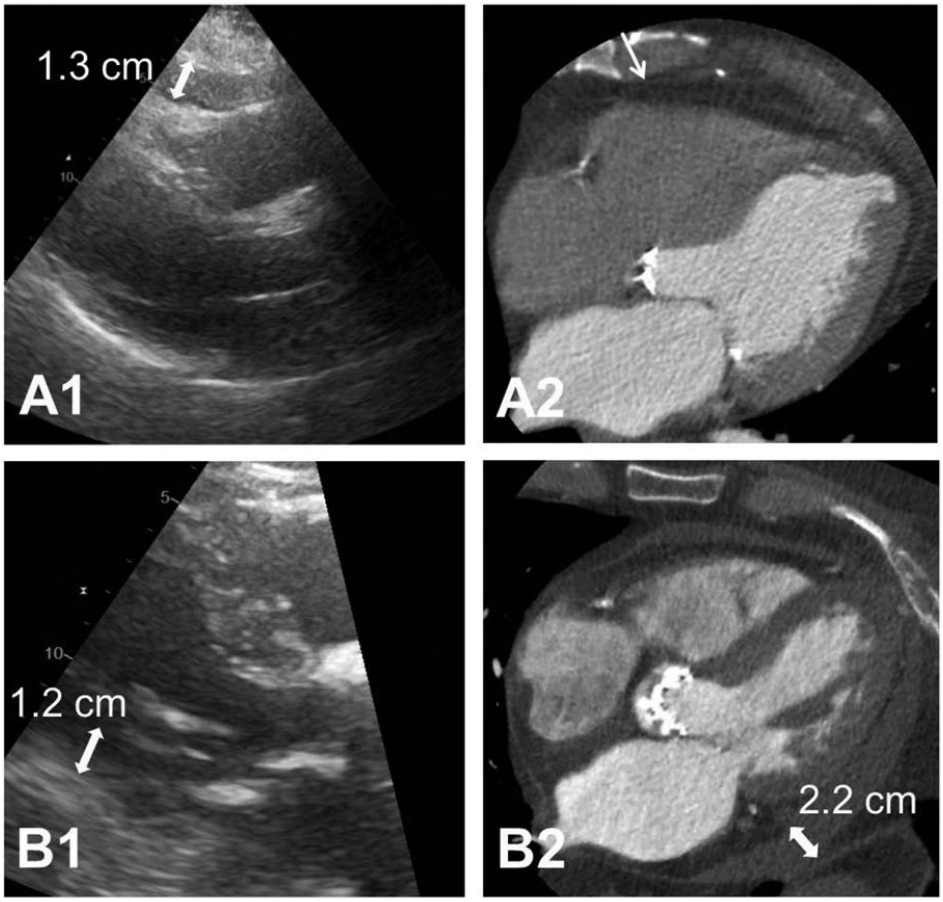
MDCT data were acquired with two scanners: an Aquilion 64 system (Toshiba Medical Systems, Otawara, Japan) and an AcquilionONE 320-detector system. For the Aquilion 64 system a collimation of 64 x 0.5 mm and a gantry rotation time of 400 ms were set. Tube current was 300-400 mA and voltage was 120 kV or 135 kV. The Acquilion ONE system used a collimation of 320 x 0.5 mm (gantry rotation time of 350 ms, tube current and voltage set at 400-580 mA and 100 kV, 120 kV or 135). Beta-blockers were administered to patients with heart rate ≥70 beats per minute, unless contraindicated. Non-ionic contrast (Iomeron 400, Bracco, Milan, Italy) was administered through the antecubital vein at a volume of 80-90 mL depending on the patient's body surface area. Data were digitally stored and analyzed with dedicated software (Vitrea2, Vital Images, Minneapolis, Minnesota, USA).

The presence of PE was assessed at 1 month follow-up, as previously described.(7) From the axial plane, the 4-chamber view was reconstructed and the largest diameter of the pericardial space in front of the right ventricle was measured. In the same plane, the largest diameter of the pericardium in the mid posterior wall of the LV was defined (Figure 1). The superior aortic recess plane - representing the pericardial cavity anterior to the aorta and the pulmonary artery- could not be reconstructed for all patients and was not systematically evaluated. Similarly to the echocardiographic classification, PE was considered small, moderate or large if any of the anterior, posterior and apical wall pericardial space was 1-10 mm, 11-19 mm or≥20 mm, respectively.

Statistical analysis

Statistical analyses were performed with a package of SPSS software version 20, (SPSS Inc., Chicago, IL, USA). Continuous variables were defined as normally or non-normally distributed according to visual inspection of the histograms, and were presented as mean and standard deviation or as median and inter-quartile range, respectively. The categorical variables were presented as number and frequencies. Categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate and p values <0.05 were considered statistically significant.

Figure 1. Transthoracic echocardiography vs. MDCT to grade PE. Panel A1 shows the para-sternal long-axis view of the left ventricle and the presence of 1.3 cm space anteriorly to the right ventricle during the entire cardiac cycle which was interpreted as moderate PE. In contrast, MDCT did not confirm the diagnosis and showed the presence of pericardial fat around the right ventricle (panel A2). Panel B1 shows the parasternal long-axis view of the left ventricle and the presence of 1.2 cm space posterior to the LV. On MDCT, the amount of PE was larger (2.2 cm) confirming the diagnosis of significant PE (panel B2). However, the echocardiography of the patient did not show any sign of cardiac tamponade.



RESULTS

A total of 293 patients (80±7 years old, 50% male) who underwent TAVI were included. Edwards SAPIEN prostheses were implanted in 260 patients (73 of 23-mm, 166 of 26-mm and 21 of 29-mm size) and CoreValve prostheses were implanted in 33 patients (1 of 23-mm, 7 of 26-mm, 24 of 29-mm and 1 of 31-mm size). Baseline characteristics of the population are outlined in Table 1.

Table 1. Baseline characteristics

	N = 293
Age (years)	80±7
Male n (%)	148 (50%)
BSA (m^2)	1.81±0.28
Creatinine (μmol/L)	88 (73-115)
Diabetes, n (%)	84 (28%)
Atrial fibrillation, n (%)	60 (21%)
Coronary artery disease, n (%)	186 (64%)
NYHA functional class III-IV, n (%)	166 (57%)
Logistic Euroscore (%)	22.3±14.0
Transfemoral n (%)	125(43%)
Transapical n(%)	168 (57%)
CoreValve n(%)	33 (11%)
Edwards SAPIEN n(%)	260 (89%)
Medication	
Beta blockers n (%)	173 (59%)
ACE inhibitors/ARBS n(%)	161 (55%)
Diuretics n (%)	180 (61%)
Spironolactone n (%)	44 (14%)
Warfarin n (%)	105 (36%)
Echocardiography	
Aortic valve area (cm^2)	0.74±0.25
Mean transaortic gradient (mmHg)	43±18
Peak transaortic gradient (mmHg)	65±27
Left ventricular ejection fraction (%)	52±14
Left ventricular end diastolic volume (ml)	106±48
Left ventricular end systolic volume (ml)	55±40

ACE, Angiotensin converting enzyme; ARB-II, Angiotensin II receptor blocker; BSA, Body surface area; NYHA, New York Heart Association

Pre-discharge echocardiography was performed after a median of 2 days (interquartile range: 1-3) after TAVI. Pre-discharge small, moderate and large PE was diagnosed in respective 217 (74.1%), 12 (4.1%) and 8 (2.7%) patients. Eight patients with clinical or echocardiographic signs of cardiac tamponade underwent pericardiocentesis. Rates of significant PE were slightly higher in patients treated through a transapical access compared with patients treated through a transfemoral access (6/168 (3.6%) vs. 2/125 (1.6%), respectively p = 0.474).

After a median follow-up of 38 days (interquartile range 31-45), 234 patients underwent repeat echocardiography. Small and moderate PE was observed in 175 (74.8%) and 8 (3.4%) patients, respectively. Severe PE was not observed in any patient. Interestingly 6 (2.5%) patients, all of them treated with transapical TAVI, who did not show any PE or had

Table 2. Agreement between transthoracic echocardiography and MDCT to grade PE at 1 month follow-up after TAVI. The classification proposed by Weitzman et al.(13) has been used.

		MDCT				
		None	**Small**	**Moderate**	**Large**	**Total**
ECHO	**None**	2	26	0	0	**28 (20%)**
	Small	7	102	1	1	**111 (77%)**
	Moderate	0	2	1	1	**4 (3%)**
	Large	0	0	0	0	**0 (%)**
	Total	**9 (6%)**	**130 (90%)**	**2 (1%)**	**2 (1%)**	**143**

ECHO, echocardiography; MDCT, multidetector computed tomography; PE, pericardial effusion.

only small PE at pre-discharge echocardiography, were diagnosed with new onset moderate PE at 1-month echocardiography. One-month follow-up MDCT data were available in 143 patients. Large PE was observed in 2 (1%) patients, moderate PE in 2 (1%) and small PE in 130 (91%) patients. In 105 patients, MDCT and echocardiography agreed on the PE grade while in the remaining 38 patients, MDCT and echocardiography disagreed (Table 2). In 29 patients, MDCT considered PE grade more severe than echocardiography: 26 patients with no PE on echocardiography had small PE on MDCT, 1 patient with small PE on echocardiography was considered having moderate PE on MDCT and 2 patients with small and moderate PE were considered having large PE on MDCT. Interestingly, patients with moderate or large PE at 1-month follow-up MDCT were hemodynamically stable and clinically asymptomatic and therefore pericardiocentesis was not performed. Among the remaining 9 patients, 7 patients with small PE on echocardiography did not show PE on MDCT and 2 patients with moderate PE on echocardiography were considered small PE on MDCT.

DISCUSSION

Significant PE early after TAVI is an uncommon complication and is more frequently observed after transapical TAVI. At follow-up, the incidence of new onset significant PE is also infrequent and is more frequently diagnosed with MDCT. Transthoracic echocardiography tends to underestimate the PE grade.

Prevalence of early and late pericardial effusion after TAVI

Clinically significant PE (including cardiac tamponade) is relatively infrequent after TAVI. While few registries report on the incidence of PE complicating TAVI(4,5,14), the incidence of new onset pericardial effusion at follow-up remains unknown. In 412 consecutive patients undergoing TAVI between 2007 and 2010 (61% transarterial and 39% transapical TAVI), Lange et al reported an incidence of early PE of 12.8%, including

2.6% of cardiac tamponade.(4) In the European Sentinel registry of TAVI, including 4571 patients who underwent transfemoral (74.2%) or transapical (16.4%) TAVI, the incidence of cardiac tamponade was 2.4%.(5) These data contrast with the incidence reported by Rezq et al which was 4.3%.(14) In the current study, we reported an incidence of cardiac tamponade similar to that reported by Lange et al and Di Mario et al.(4,14) Differences related to patient characteristics and procedural technique may account for the disparate incidences. For example, Rezq et al reported a higher incidence of cardiac tamponade among patients in whom a right ventricular screw-in lead was implanted compared with patients in whom a passive temporary pacemaker wire was used.(14) In addition, the use of stiff Amplatzer wires that provide excellent support during the deployment of the valve has been associated with LV tears that can cause fatal cardiac tamponade.(14) Careful manipulation of the wires and delivery systems within the LV is crucial to avoid this complication. Besides perforation of the RV or LV free walls by temporary pacemaker wires or delivery systems, other causes of cardiac tamponade include aortic annulus rupture after deployment of balloon-expandable valves, aortic dissection and complications of transapical access, such as LV tears. The majority of these causes leads to the development of cardiac tamponade immediately during the procedure or within few hours after the procedure.(14) In contrast, late PE after TAVI is less common and might be related with chronic aggressive anticoagulation treatments or post-pericardiotomy syndrome (in transapical TAVI). The incidence of new onset late PE in the present evaluation was 2.5% and was observed only in patients who underwent transapical TAVI. Importantly, hemodynamically significant late PE was not observed in any patient. The cause of this new onset PE at 1 month follow-up remains speculative, but post-pericardiotomy syndrome may be the most plausible cause since it was observed only in a patient undergoing transapical TAVI.

Multimodality imaging approach to evaluate pericardial effusion after TAVI

Echocardiography is the imaging technique of first choice to diagnose significant PE complicating TAVI. During the procedure, the use of transesophageal echocardiography permits immediate diagnosis of PE and cardiac tamponade. However, the number of TAVI procedures that are being performed with sedation instead of general anaesthesia is growing and the only imaging modality that can be used is transthoracic echocardiography. The present study highlights the discrepancies between transthoracic echocardiography and MDCT in grading PE. Late after TAVI, transthoracic echocardiography underestimated the PE grade compared with MDCT. This observation may be relevant in patients who underwent transapical TAVI in whom a suboptimal acoustic window may challenge the diagnosis. Compared to transthoracic echocardiography, MDCT may provide higher diagnostic accuracy for loculated PE and permits differentiation between subepicardial fat and PE. In addition, MDCT may elucidate the cause of late new onset PE

such as pseudoaneurysms of the LV apex after transapical TAVI.(15) However, large PEs are hardly missed by transthoracic echocardiography which provides also hemodynamic assessment of cardiac function and permits accurate diagnosis of cardiac tamponade.

Limitations

Some limitations should be acknowledged. The present evaluation concerns retrospective analysis of data clinically acquired in a single center. The number of patients diagnosed with moderate or severe PE was small. The percentage of patients undergoing transapical TAVI was considerably high and therefore, the results of the present study may not be generalizable.

CONCLUSIONS

Significant PE early after TAVI is infrequent. The prevalence of small and moderate PE remains stable at 1 month follow-up. MDCT refines the diagnosis of significant PE. The clinical implications of the discrepancies in the quantification of PE between imaging modalities remain unclear. Further studies are needed to elucidate which patients should be evaluated with MDCT to diagnose the presence and cause of significant PE at follow-up.

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Part II

Transcatheter aortic valve implantation in specific subpopulations

Chapter 6

Impact of Valvulo-Arterial Impedance on 2-year Outcome of Patients Undergoing Transcatheter Aortic Valve Implantation

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ABSTRACT

Background: Elderly patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) often have increased calcification and fibrosis of the aorta. Indices that account for the severity of valvular obstruction and systemic vascular impedance may better assess the total left ventricular afterload. The present study evaluated changes in valvulo-arterial impedance (Zva), systemic arterial compliance and systemic vascular resistance after TAVI and investigated the prognostic value of these parameters. **Methods:** A total of 116 patients (49% men, 81±8 years) with symptomatic severe aortic stenosis underwent TAVI. Zva, systemic arterial compliance and systemic vascular resistance were measured at baseline, 1 and 12 months after TAVI. The primary endpoint was all-cause mortality. **Results:** After TAVI, there was a significant reduction in Zva (from 5.40±1.52 mmHg/mL/m^2 at baseline to 4.13±1.17 at 1 month and to 4.35±1.38 at 1 year, $p < 0.001$). Systemic arterial compliance (from 0.57±0.27 ml/m^2/mmHg to 0.57±0.28 and to 0.53±0.27; $p = 0.408$) and systemic vascular resistance (from 1938±669 dyne.s.cm^{-5} to 1856±888 and to 1871±767; $p = 0.697$) did not change significantly over time. During a median follow-up of 25 months, survival rates of patients with baseline Zva ≥5 mmHg/mL/m^2 were lower compared with patients with Zva <5 mmHg/mL/m^2 (82% vs. 91%, respectively; log-rank $p = 0.04$). On multivariate Cox proportional hazards analysis, baseline Zva was independently associated with all-cause mortality (HR = 1.48, 95% CI = 1.05-2.07, $p = 0.025$).**Conclusions:** In patients undergoing TAVI there is a significant post-procedural reduction in Zva but not in systemic arterial compliance or vascular resistance. Baseline Zva is an independent predictor of overall mortality at 2 years follow-up.

INTRODUCTION

The PARTNER trial and many registries have confirmed the safety and efficacy of transcatheter aortic valve implantation (TAVI) in over 60,000 patients with symptomatic severe aortic stenosis and high risk or contraindications for surgery.(1-6) TAVI improves aortic valve hemodynamics, systolic left ventricular (LV) function and clinical outcome.(7-10) In addition, significant regression in LV hypertrophy has been reported in patients with aortic stenosis following TAVI.(8,11) However, there is an important inter-individual variability in LV mass regression following surgical aortic valve replacement. In particular, older patients tend to show less LV mass reduction and more impaired LV diastolic function after aortic valve replacement compared with younger patients.(12-14) Sustained LV hypertrophy and diastolic dysfunction after aortic valve replacement have a negative impact on the long-term outcome of patients undergoing aortic valve replacement.(12) The lack of a straightforward relationship between stenosis-dependent pressure overload relief and LV mass reduction after aortic valve replacement has led to further search for additional pathophysiological determinants of LV geometry and function after aortic valve replacement. For example, sustained reduced systemic arterial compliance may hinder the beneficial effects of aortic valve replacement on LV function and hypertrophy regression.(15) Older patients with calcific aortic stenosis often have reduced systemic arterial compliance due to concomitant arterial atherosclerosis and/or medial elastocalcinosis. This reduced systemic arterial compliance contributes to increased LV afterload imposed by the valvular stenosis. The valvulo-arterial impedance (Zva) has been proposed to assess the global (i.e. valvular + arterial) load imposed to the LV.(16,17) Severely increased Zva has been associated with reduced survival in the aortic stenosis population treated conservatively.(18) Patients who are candidate for TAVI often have severely reduced systemic arterial compliance and increased Zva which can reduce early after TAVI.(19) However, the influence of Zva on TAVI outcomes has not been explored. The objectives of the present study were two-fold: 1) to assess changes in Zva, systemic arterial compliance and systemic vascular resistance at 1 and 12 months following TAVI and 2) to assess the impact of baseline Zva on survival after TAVI.

METHODS

Patient population

A total of 116 patients with severe symptomatic aortic stenosis (aortic valve area < 1.0 cm^2 or transaortic mean pressure gradient ≥40 mmHg) who underwent TAVI in two centers (84 patients in the Leiden University Medical Center, Leiden, The Netherlands and 32 patients in the Québec Heart and Lung Institute, Department of Medicine, Laval

University, Québec, Canada) were included in the present study. Patients who underwent transcatheter valve-in-valve procedures or in whom baseline Zva could not be derived were excluded. Based on the evaluation of a multidisciplinary team, patients were considered for TAVI due to high predicted operative risk or contraindications for conventional surgical aortic valve replacement.(20) According to the institutional protocols, patients underwent comprehensive clinical and echocardiographic evaluation prior to TAVI. In addition, invasive coronary angiography was performed to rule out significant coronary artery disease amenable to percutaneous intervention.

Clinical and echocardiographic data were retrospectively analyzed. Clinical parameters included demographics, cardiovascular risk factors, clinical symptoms, medications and operative mortality risk calculated according to the logistic European system for cardiac operative risk evaluation (EuroSCORE I).(21) Non-invasive parameters of aortic stenosis severity and vascular resistance, including Zva and systemic arterial compliance, were measured and the changes in these parameters at short- and mid-term follow-up after TAVI were evaluated. In addition, the independent associations of these parameters with TAVI outcomes were investigated.

Echocardiography

Transthoracic echocardiography (TTE) was performed at baseline with commercially available ultrasound systems (Vivid 7, E9, General Electric, Horten, Norway; ie33 Phillips Medical Systems). The aortic valve anatomy (bicuspid or tricuspid) was evaluated in the parasternal short-axis view. Aortic jet velocity was evaluated in multiple acoustic windows, adjusting gain, wall filter, baseline and scale of continuous wave Doppler recordings to optimize the signal. The LVOT velocity was measured in the apical long-axis or 5-chamber views from the pulsed wave Doppler spectral signal.(22) Aortic valve area (AVA) was calculated with the continuity equation.(22) Severe aortic stenosis was considered when the AVA was <1.0 cm^2 and/or the transaortic mean gradient was ≥40-50 mmHg.(23,24) Left ventricular (LV) end-diastolic (LVEDV) and end-systolic volumes (LVESV) were measured according to the biplane Simpson's method and these measures were used to calculate the LV ejection fraction (LVEF).(25) Standard LV linear dimensions and LV mass were also measured according to current recommendations.(25) Finally, LV stroke volume was measured in the LV outflow tract from the pulsed wave Doppler recordings and indexed to body surface area (SVi).

Measurement of systemic arterial compliance, valvulo-arterial impedance and systemic vascular resistance

Systemic arterial compliance was calculated as the ratio of LV SVi to pulse pressure as previously described.(26) Systemic arterial pressure was measured with an arm-cuff sphygmomanometer at the time of echocardiography and the pulse pressure was cal-

culated from the difference between systolic and diastolic arterial pressures. In addition, global LV hemodynamic load was estimated with the use of the Zva calculated from the formula: (systolic arterial pressure + transaortic mean gradient)/SV index.(16) Based on previous studies, LV global load was considered to be severely increased when the value of Zva was ≥5 mm Hg/ml/m^2.(16) Moreover, systemic vascular resistance was calculated with the formula: (80 × mean arterial pressure)/cardiac output.(16,18)

TAVI procedure

At the catheterization laboratory or hybrid operating room, an Edwards SAPIEN prosthetic valve (Edwards Lifesciences Inc., CA, USA) of either 23 mm or 26 mm size was implanted under general anesthesia. Prosthesis size selection was based on dimensions of the aortic valve annulus as assessed with transesophageal echocardiography or multidetector row computed tomography, if available. Either a transapical or transfemoral approach was used, based on the peripheral artery anatomy as assessed with imaging of the ilio-femoral arteries and aorta.(27) The technique included rapid ventricular pacing during balloon dilatation of the native aortic valve and deployment of the balloon-expandable prosthetic valve.(27) Transesophageal echocardiography complemented fluoroscopy for better guidance of the procedure. Procedural success was defined as successful implantation of a functioning aortic prosthesis without intra-procedural mortality.

Follow-up

Clinical and echocardiographic follow-up was scheduled at 1 and 12 months after TAVI. Clinical evaluation included New York Heart Association (NYHA) functional class and complete TTE was performed to assess prosthetic valve hemodynamics, LV dimensions and function as well as Zva, systemic arterial compliance and systemic vascular resistance. Paravalvular aortic regurgitation was evaluated at one month follow-up and was graded none or trivial (0-1), mild (2+), moderate (3+) or severe (4+), according to recommendations. (28) In addition, all-cause mortality was recorded during follow-up.

Statistical analysis

Statistical analyses were performed using SPSS software version 17, (SPSS Inc., Chicago, IL, USA) and STATA software, version 11 (Stata Corp, College Station, TX, USA). Continuous variables are presented as mean and standard deviation if normally distributed, as determined by visual inspection of their histogram, or median and interquartile range otherwise. Categorical variables are presented as frequencies and percentages. Continuous variables were compared using unpaired Student's t-test or the Mann-Whitney test where appropriate, whereas categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Changes in continuous variables in overall population

from baseline to follow-up were analyzed with repeated measures analysis of variance (ANOVA), and Bonferroni's correction was used for post-hoc analysis of significant results. In addition, patients were dichotomized according to a baseline value of Zva ≥5 mmHg/ml/m^2 or <5 mmHg/ml/m^2. One-way ANOVA analysis for repeated measures was used to compare echocardiographic changes between groups. Cumulative events rates were calculated using the Kaplan-Meier method for patients with a Zva ≥5 mmHg/ml/m^2 and patients with a Zva <5 mmHg/ml/m^2 at baseline. The log-rank test for time-to-event data with respect to all-cause mortality endpoint was used for statistical comparison between 2 patient groups. Additionally, univariate and multivariate Cox proportional hazards models were performed to identify independent determinants of all-cause mortality. The estimated hazard ratios and the 95% confidence intervals were obtained. Univariate variables with a $p < 0.2$ were included in the multivariate model. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

A total of 116 patients with severe symptomatic aortic stenosis (mean age 81±8 years old, 49% men) were evaluated. All patients underwent successful TAVI using a transfemoral (n = 48, 41%) or transapical (n = 68, 59%) approach. Thirty-five patents (30%) received a 23-mm valve prosthesis and 81 (70%) received a 26-mm valve. Clinical and procedural characteristics are outlined in Table 1.

Table 1. Patient characteristics

Variable	N = 116
Age (years)	81±8
Male, n (%)	57(49%)
BSA (m^2)	1.78±0.20
Renal dysfunction (Creatinine>1.2 mg/dl)	41(35%)
Hypertension, n (%)	48 (41%)
Hypercholesterolemia, n (%)	63 (54%)
Diabetes, n (%)	32 (27%)
Peripheral vascular disease, n (%)	26(22%)
Smoking, n (%)	40 (35%)
Coronary artery disease, n (%)	75 (65%)
NYHA functional class III-IV, n (%)	85 (73%)
Pacemaker, n(%)	8 (7%)
Atrial fibrillation, n (%)	27 (23%)

Table 1. Patient characteristics (continued)

Medications (n, %)	
Beta-blockers	44 (38%)
Diuretics	76 (65%)
Statins	77 (66%)
Ca-antagonists	36 (31%)
Logistic EuroSCORE I	21.2±12.3
Transfemoral / Transapical TAVI, n(%)	48(41%) / 68(59%)
Sapien-Edwards valve, n(%)	
23 mm	35 (30%)
26 mm	81 (70%)

Abbreviations: BSA=Body surface area; NYHA=New York Heart Association; TAVI: transcatheter aortic valve implantation

Changes in aortic valve hemodynamics and global LV load after TAVI

During the first postoperative month, 7 (6%) patients died and 3 additional patients died within the first postoperative year. Overall 21 patients died during a median follow-up of 25 months follow-up (interquartile range: 13-45 months) and there were no patients lost at follow-up. Echocardiographic assessment was available in 109 patients at first month follow-up and complete data (baseline, 1 and 12 months after TAVI) were available in 100 patients. Six patients had been followed-up for less than 12 months.

Table 2 summarizes the changes in aortic valve hemodynamics, LV dimensions and function, Zva, systemic arterial compliance or vascular resistance. As expected, AVA significantly increased (from 0.67±0.17 cm^2 to 1.86±0.49 cm^2 at 1 month follow-up and remained stable at 12 months follow-up: 1.81±0.61 cm^2, $p < 0.001$) and transaortic mean pressure gradient significantly decreased after TAVI (baseline 42±15 mmHg to 8±3 mmHg and 9±5 mmHg at 1 and 12 months follow-up, respectively; $p < 0.001$). LVEF increased slightly from 54±14% to 55±13% at 1 month and to 56±11% at 12 months ($p = 0.051$). There was a significant reduction in Zva (from 5.40±1.52 mmHg/mL/m^2 to 4.13±1.17 mmHg/mL/m^2 at 1 month follow-up and remained stable at 12 months: 4.35±1.38 mmHg/mL/m^2, $p < 0.001$) (Figure 1). In contrast, systemic arterial compliance did not change significantly (from 0.57±0.27 ml/m^2/mm to 0.57±0.28 ml/m^2/mmHg and to 0.53±0.27 ml/m^2/mmHg, $p = 0.408$) (Table 2). Similarly, systemic vascular resistance did not change over time (from 1938±669 dyne.s.cm^{-5} to 1856±888 dyne.s.cm^{-5} and to 1871±767 dyne.s.cm^{-5}, $p = 0.697$).

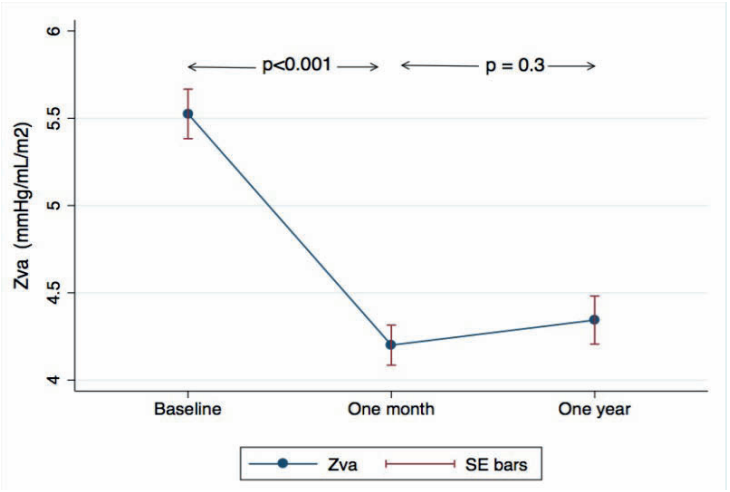
In addition, the incidence of paravalvular aortic regurgitation was evaluated at 1 month follow-up. None or trivial PAVR was observed in 82%, mild in 17 (16%) and severe in 2 (2%) patients.

Table 2. Changes in echocardiographic parameters after TAVI

	Baseline	1 month	12 months	p- value
AVA (cm^2)	0.67±0.17	1.86±0.49	1.81±0.61	<0.001
MG (mmHg)	42±15	8±3	9±5	<0.001
LVEDV (ml)	117±45	117±45	110±41	0.065
LVESV(ml)	56±38	55±39	48±29	0.002
LV SV index(ml/m^2)	34±10	34±9	35±11	0.725
LVEF (%)	54±14	55±13	56±11	0.051
LV mass (g)	232±60	224±66	201±47	<0.001
Zva ($mmHg/mL/m^2$)	5.40±1.52	4.13±1.17	4.35±1.38	<0.001
Zva5≥ $mmHg/mL/m^2$, (%)	57%	24%	24%	<0.001
SAC ($ml/m^2/mmHg$)	0.57±0.27	0.57±0.28	0.53±0.27	0.408
SAC<0.6 $ml/m^2/mmHg$, (%)	67%	67%	71%	0.456
SVR (dyne.s cm^{-5})	1938 ± 669	1856 ±888	1871 ± 767	0.697
SAC>2000 dyne.s cm^{-5}, (%)	37%	26%	34%	0.642
SBP (mmHg)	133±23	138±24	142±23	0.001
DBP (mmHg)	69±12	69±10	70±13	0.914
PP (mmHg)	64±20	69±22	73±21	0.453
Cardiac output (L/min)	4.0±1.2	4.4±1.3	4.5±1.4	0.033

Abbreviations: AVA=aortic valve area; DBP=diastolic blood pressure LV=left ventricle; LVEDV=left ventricular end-diastolic volume; LVEF= LV Ejection Fraction; LVESV=left ventricular end-systolic volume MG=mean gradient; PP= pulse pressure; SAC=systemic arterial compliance; SBP= systolic blood pressure; SVR=systemic vascular resistance; Zva=valvulo-arterial impedance

Figure 1. Mean values of global LV afterload (Zva) at baseline, 1 month and 12 months follow-up (unit $mmHg/m^L/m2$).



Changes in symptoms and global LV load after TAVI according to baseline Zva

At baseline, 68 (57%) patients had a Zva ≥5 mmHg/ml/m^2. Table 3 outlines the differences in clinical and echocardiographic parameters between patients with baseline Zva ≥5 mmHg/ml/m^2 and patients with Zva <5 mmHg/ml/m^2. Patients with baseline Zva ≥5 mmHg/ml/m^2 had smaller AVA (0.65±0.18 cm^2 vs. 0.73±0.18 cm^2 p = 0.020), lower systemic arterial compliance (0.45 ± 0.15 ml/m^2/mmHg vs. 0.72±0.29 ml/m^2/mmHg; p < 0.001), smaller LVEDV (105±34 ml vs. 133±50 ml, p = 0.001), lower SVi (28±6 ml/m^2 vs. 41±9 ml/m^2,

Table 3. Baseline clinical and echocardiographic parameters of patients with Zva≥5 mmHg/m^L/m2 versus patients with Zva<5 mmHg/m^L/m2 at baseline

	Zva ≥5 (n = 68)	Zva <5 (n = 48)	p-value
Age (years)	80 ± 9	82 ± 8	0.303
Male, n (%)	30 (44)	27(56)	0.198
BSA (m^2)	1.8±0.2	1.75±0.21	0.310
Diabetes n (%)	18 (27)	14 (29)	0.749
Renal dysfunction n (%)	21 (31)	20 (42)	0.231
Hypertension n (%)	33 (49)	15 (31)	0.063
Coronary artery disease n (%)	31(27)	44 (38)	0.989
Pacemaker n (%)	3 (4)	5 (10)	0.238
Atrial fibrillation n (%)	20 (29)	7 (14)	0.063
NYHA III-IV n (%)	47 (69)	38 (79)	0.228
Logistic EuroSCORE	21.6±12	20.8±12.8	0.749
Beta-blockers	29(43%)	15(31%)	0.213
Diuretics	44(65%)	32(67%)	0.827
Ca-antagonists	19(28%)	17(35%)	0.391
ACE inhibitors/ARBS	35(51%)	26(54%)	0.775
AVA (cm^2)	0.65±0.18	0.73±0.18	0.020
MG (mmHg)	42±16	41±16	0.664
PG (mmHg)	67±22	65±23	0.726
LVEDV (ml)	105±34	133±50	0.001
LVESV (ml)	53±36	61±42	0.335
LVEF ≤35%	12(18%)	5(10%)	0.278
SVi (ml/ m^2)	28±6	41±9	<0.001
SVi≤35 ml/ m^2	61(89%)	11(23%)	<0.001
SAC (ml/ m^2/mmHg)	0.45 ± 0.15	0.72±0.29	<0.001
SBP (mmHg)	137±24	128±22	0.040
PP (mmHg)	65±20	61±18	0.181
SVR (dyne.s cm^{-5})	2192 ± 709	1579± 455	0.005
LV mass (g)	235±74	231±74	0.788
Cardiac output (L/min)	3.6	4.7	<0.001

Abbreviations: see table 2

p < 0.001) and higher systemic vascular resistance (2192 ± 709 dyne.s.cm^{-5} vs. 1579± 455 dyne.s.cm^{-5}, p = 0.005) compared with patients with Zva <5 mmHg/ml/m^2.

The percentage of patients with low gradient aortic stenosis (mean gradient <40 mmHg) was similar in patients with Zva ≥5 mmHg/mL/m^2 and patients with Zva <5 mmHg/mL/m^2 (33 [48%] vs. 23 [48%], respectively; p = 0.948). The percentage of patients with low gradient aortic stenosis and preserved LVEF (≥50%) was also similar between groups (17 (25%) in patients with Zva ≥5 mmHg/mL/m^2 vs. 16 (33%) in patients with Zva<5 mmHg/mL/m^2, p = 0.327).

Overall 86 (86%) of patients that were followed up at 12 months improved their functional capacity by at least 1 grade. There was no difference in the proportion of patients that improved clinically between the group of patients with a baseline Zva ≥5 mmHg/mL/m^2 and patients with Zva <5 mmHg/mL/m^2 (50 [85%] vs. 36 [86%]), respectively; p = 0.944).

In terms of echocardiographic outcomes, patients with baseline Zva <5 mmHg/mL/m^2 showed a significant reduction in LVEDV as compared with patients with Zva ≥5 mmHg/mL/m^2 (from 133±52 ml to 122±55 ml and to 111±50 ml at 1 and 12 months follow-up vs. 104±32 ml to 113±35 ml and to 109±32 ml, respectively; p = 0.001). Interestingly, patients with baseline Zva ≥5 mmHg/mL/m^2 showed a significant improvement in LVEF (from 52±14% to 54±13% and to 57±11% at 1 and 12 months follow-up vs. 55±13% to 56±13% and to 55±11%, respectively; p = 0.037) and SVi (from 28±6 ml/m^2 to 33±9 ml/m^2 and to 35±8 ml/m^2 at 1 and 12 months follow-up vs. 41±9 ml/m^2 to 37±7 ml/m^2 and to 36±10 ml/m^2, respectively; p < 0.001) (Table 4). A subanalysis focused on 72 patients with baseline SVi≤35 ml/ m^2 showed no differences in remodeling between groups (Table 5).

Table 4. Changes in echocardiographic parameters according to ZVa values

	Zva ≥5 mmHg/mL/m^2 (n = 58)			**Zva <5 mmHg/mL/m^2 (n = 42)**			**p-value between groups**	**p-value interaction group and time**
	Baseline	**1 month**	**12 months**	**Baseline**	**1 month**	**12 months**		
LVEDV(ml)	104±32	113±35	109±32	133±52	122±55	111±50	0.089	0.001
LVESV(ml)	52±32	51±32	44±24	60±44	58±47	51±32	0.306	0.065
LVEF (%)	52±14	54±13	57±11	55±13	56±13	55±11	0.740	0.037
LV mass(g)	228±71	219±62	200±49	237±72	231±71	203±55	0.510	0.562
SVi (ml/m^2)	28±6	33±9	35±8	41±9	37±7	36±10	0.001	0.001
SAC (ml/m^2/ mmHg)	0.45±0.16	0.51±0.24	0.52±0.21	0.73±0.29	0.65±0.30	0.52±21	0.356	0.002
SVR (dyne.s cm^{-5})	2194±689	1971±899	1937±822	1605±469	1707±861	1785±690	0.001	0.087
SBP (mmHg)	137±26	135±18	140±24	126±28	130±29	139±28	0.470	0.442
Cardiac output (L/min)	3.6±0.9	4.3±1.4	4.5±1.5	4.6±1.38	4.7±1.2	4.5±1.3	0.015	0.007

Abbreviations: see table 2.

Table 5. Changes in echocardiographic parameters in 72 patients with baseline SVi≤35 ml/m²

	Zva ≥5 mmHg/mL/m² (n = 61)			Zva <5 mmHg/mL/m² (n = 11)			p- value between groups	p- value, interaction group and time
	Baseline	1 month	12 months	Baseline	1 month	12 months		
LVEDV (ml)	102±30	111±34	109±33	105±61	111±61	112±56	0.859	0.829
LVESV (ml)	52±30	50±29	44±23	57±60	57±54	52±37	0.447	0.119
LVEF (%)	52±14	55±13	58±11	51±19	56±16	53±13	0.128	0.283
SVi (ml/m²)	27±5	33±9	33±9	30±7	35±6	36±15	0.416	0.835
LV mass (g)	222±68	216±61	198±50	200±68	203±64	201±54	0.113	0.059

Abbreviations: see table 2.

Effect of baseline Zva on all-cause mortality

During a median follow-up of 25 months (interquartile range: 13-45 months), a total of 21 (18%) patients died. The Kaplan–Meier curves show the survival rates for patients divided according to the baseline Zva value (≥5 mmHg/ml/m² vs. <5 mmHg/m/ m²) (Figure 2). The survival rates at 1 and 2 years follow-up in the group of patients with baseline Zva ≥5 mmHg/mL/m² were 88% and 82% respectively, compared with the 96% and 91%, for the group of patients with Zva <5 mmHg/mL/m² (log-rank p = 0.04). From the univariate Cox proportional hazards analysis, baseline values of Zva (HR = 1.52 95% CI = 1.16-1.99, p = 0.002), LV mass (HR = 1.00, 95% CI = 0.99-1.01, p = 0.118) and systemic vascular resistance (HR = 1.05 per each 100 dyne.s cm^{-5} increase, 95% CI = 1.01-1.11, p = 0.044) were selected to be included in the multivariable analysis (Table 6). In the multivariate model only baseline Zva was independently associated with all-cause mortality (HR = 1.48, 95% CI = 1.05-2.07, p = 0.025).

Figure 2. Kaplan-Meier curves of survival of patients with baseline Zva≥5 mmHg/m^{L}/m2 and patients with Zva<5

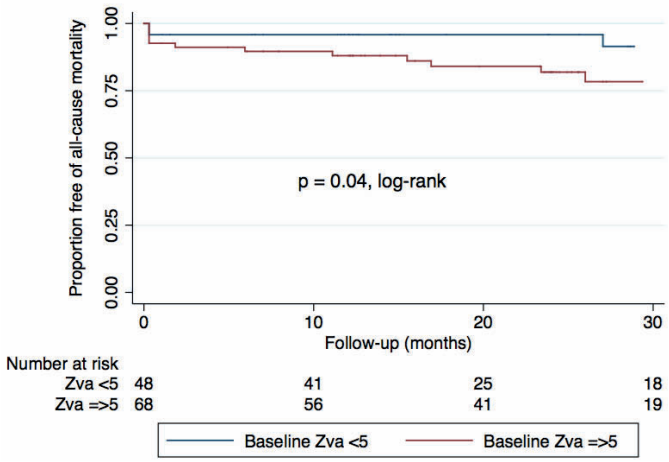


Table 6. Univariate and multivariate Cox proportional hazards model to predict all-cause mortality

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Zva (per 1 mmHg/mL/m^2 increase)	1.52 (1.16-1.99)	0.002	1.48 (1.05-2.07)	0.025
Male	1.42 (0.60-3.38)	0.421		
Diabetes	1.66 (0.66-4.18)	0.279		
Renal dysfunction	1.01 (0.42-1.46)	0.982		
Coronary artery disease	0.64 (0.26-1.53)	0.319		
Aortic mean gradient (per 1 mmHg increase)	0.99 (0.96-1.02)	0.515		
LVEF (per 1% increase)	0.99 (0.96-1.02)	0.759		
LVEDV (per 1 ml increase)	0.99 (0.98-1.00)	0.691		
NYHA ≥III	1.54 (0.44-5.34)	0.493		
LV mass (per 1 g increase)	1.00 (0.99-1.01)	0.118	1.00 (0.99-1.01)	0.075
SAC (per 1 ml/m^2/mmHg increase)	0.51(0.07-3.47)	0.429		
SVR (per 100 dyne.s cm^{-5} increase)	1.05 (1.01-1.11)	0.044	1.01 (0.93-1.10)	0.711
Log Euroscore (%)	0.97 (0.94-1.01)	0.245		

Abbreviations: LV=Left ventricle, LVEF=LV ejection fraction; LVEDV=LV end-diastolic volume; NYHA=New York Heart Association; SAC=systemic arterial compliance; SVi= stroke volume index; SVR=systemic vascular resistance; Zva=valvulo-arterial impedance.

DISCUSSION

The present study showed that TAVI leads to improved valvular hemodynamics, with significant reductions in systolic pressure gradients and increase in aortic valve area, and significant reduction in LV global pressure overload, as measured with Zva. In contrast, systemic arterial compliance and systemic vascular resistance did not change significantly following TAVI. Baseline Zva was independently associated with late outcomes (all-cause mortality) after TAVI.

Changes in global LV pressure afterload in patients undergoing TAVI

TAVI leads to improved aortic valve hemodynamics and LV systolic function, significant reductions in LV mass and improved survival.(7-9,29) In terms of valvular hemodynamic improvements, the majority of previous series have evaluated systolic transvalvular pressure gradients and aortic valve area. However, valvular parameters reflect only one aspect of the LV hemodynamic load.(16) Systemic arterial compliance and vascular resistance are important contributors to increased LV hemodynamic load in patients with aortic stenosis. The Zva is a valid marker of global LV hemodynamic burden in these patients.(16) The present study shows that the majority of patients with severe aortic stenosis undergoing TAVI had a markedly increased Zva (≥5 mmHg/mL/m^2) which significantly decreased after TAVI. This reduction was mainly determined by a significant

increase in AVA and associated decrease in gradient and not by an improvement in systemic arterial compliance or vascular resistance. Indeed, these vascular hemodynamic parameters were severely abnormal in the vast majority of the patients at baseline and remained unchanged after TAVI. These results were expected since patients undergoing TAVI may have significant arterial atherosclerosis and/or medial elastocalcinosis that lead to impaired systemic arterial compliance and increased vascular resistances. The TAVI procedure only addresses the valvular problem and not the vascular pathologic processes. Hence it is unlikely that TAVI yields normalization of systemic arterial compliance and systemic vascular resistance in elderly patients with associated co-morbidities, such as chronic renal dysfunction, hypertension and diabetes. Similar results were described by Giannini et al in a series of 102 patients undergoing TAVI,(19) in which significant reductions in Zva were observed early after TAVI.(19) In contrast, the authors also reported significant acute improvement in systemic arterial compliance and reduction in systemic vascular resistance. These conflicting results may be explained by the differences in the baseline characteristics of the patient populations. The study population of Giannini and coworkers included a higher proportion of patients with impaired baseline LVEF and the vascular arterial hemodynamics (i.e. systemic arterial compliance and vascular resistance) were impaired to a lesser extent in the study of Giannini et al. than in the present population. These findings suggest that the presence of more advanced vascular disease may limit the beneficial effects of aortic valve replacement.

Valvulo-arterial impedance to predict prognosis after TAVI

Previous studies have demonstrated the prognostic value of Zva in asymptomatic aortic stenosis patients with preserved LV ejection fraction.(18,30,31) However, a recent multicenter study of patients with low-ejection fraction, low-gradient aortic stenosis reported that Zva did not have incremental prognostic value.(32) In this subgroup of patients, Zva may not be an accurate parameter to estimate global LV afterload since subtle changes in SVi or heart rate may cause significant variations in Zva.(33) However, the prognostic value of Zva remains unknown in patients with increased operative risk or contraindications for surgical aortic valve replacement who are candidates for TAVI. In the study by Giannini et al. patients who died early after TAVI had higher Zva compared with patients who were alive at 6 months after TAVI.(19) The present study further demonstrates that Zva at baseline is an independent predictor of all-cause mortality in severe aortic stenosis patients treated with TAVI. These results are in agreement with the study by Hachicha et al where Zva was also an independent determinant of clinical outcome regardless of the treatment (surgical aortic valve replacement or medical treatment).(34) Zva remained independently associated with increased mortality despite adjusting for systemic vascular resistance, thereby suggesting that other factors may contribute to this association. Indeed, high baseline Zva may reflect severe valvular disease and

hemodynamic load that may not be completely corrected by TAVI. Patients with high Zva often have smaller LV cavity and aortic annulus and potentially more calcified aortic valve cusps and may be at higher risk for prosthesis-patient mismatch, i.e. residual aortic stenosis after TAVI.(9,35) Finally, high Zva may be a marker of more advanced myocardial fibrosis and dysfunction. Herrmann et al. have reported that Zva correlates well with the extent of myocardial fibrosis and systolic longitudinal shortening.(36) Patients with severe myocardial fibrosis and associated impaired LV longitudinal kinetics had higher mortality and less improvement of symptomatic status after surgical aortic valve replacement.

Clinical implications of implementing valvulo-arterial impedance measurement in routine clinical practice

So far, current guidelines recommend aortic valve replacement in patients with severe symptomatic aortic stenosis as defined by AVA, mean transaortic pressure gradient and maximum peak systolic velocity.(23) However, these hemodynamic parameters reflect only one component of the global (i.e. valvulo-arterial) LV pressure overload. Systemic arterial compliance and vascular resistance are not taken into consideration in current guidelines. In elderly patients with high prevalence of hypertension, coronary artery disease and atherosclerosis, the inclusion of these parameters may help to refine risk stratification. In patients who are deemed not operable, TAVI is a feasible and safe therapeutic alternative. However, in order to improve the outcomes of this therapy, accurate patient selection is crucial. The inclusion of Zva in the risk stratification may help to identify the patients who may be at higher risk for poor outcome following TAVI. Additional studies are warranted to elucidate whether the inclusion of a measure of global LV hemodynamic load, such as Zva, in clinical operative risk scores may help to improve the outcomes of patients undergoing TAVI.

Limitations

The present patient population and the number of patients reaching the endpoint are rather small. In addition, the study design is retrospective. In addition, assessment of pseudo-severe aortic stenosis with stress echocardiography was not systematically performed. Atrial fibrilation was more commonly observed in the group of patients with Zva $\geq$5 mmHg/mL/m^2. Although in these patients SVi was averaged from several heart beats, calculation of Zva is flow-dependent and a systematic error may have been introduced. Furthermore procedural complications were not evaluated according to Valve Academic Research Consortium criteria. The present results need to be confirmed in larger series of patients and the impact of Zva on TAVI outcomes should be validated in a prospective study.

CONCLUSIONS

In patients undergoing TAVI there is a significant post-procedural reduction in Zva but not in systemic arterial compliance or vascular resistance. High baseline Zva is an independent predictor of increased all-cause mortality at 2-year follow-up. Further studies are needed to identify the role of the routine measurement of ZVa for the identification of patients who have a high likelihood to benefit from TAVI.

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Chapter 7

Quantitative analysis of changes in mitral regurgitation after transcatheter aortic valve implantation

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ABSTRACT

Patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) often have concomitant significant mitral regurgitation (MR). Quantification and time course characterization of changes in MR after TAVI remain unexplored. The present study evaluated quantitatively assessed changes of significant MR after TAVI.

Fifty-nine patients (age 82±6 years, male 41%) with severe aortic stenosis and mild or more MR undergoing TAVI were evaluated retrospectively. All patients underwent pre-discharge echocardiography and 44 underwent repeat echocardiography at 12 months follow-up. Mitral regurgitation was quantitatively assessed. Improvement in MR, defined as ≥30% reduction in effective regurgitant orifice area (EROA), was assessed in the pre-discharge echocardiogram or at 12 months follow-up. Mitral regurgitant volume reduced from 35.6[2.2] to 18.0[1.8] and to 17.5[2.4] ml ($p < 0.001$), EROA from 20.5 [1.1] to 13.9[1.2] and to 10.6[1.2] mm^2 ($p < 0.001$) and vena contracta from 5.0 [0.15] to 3.8 [0.18] and to 3.5 [0.24] mm ($p < 0001$) immediately after TAVI and at 12 months, respectively. Overall, 35 (59%) patients showed a pre-discharge improvement in MR and an additional 10 (17%) improved by 12 months post-TAVI. In multivariable analysis, baseline EROA (odds ratio 1.095, 95% confidence interval: 1.013-1.185, $p = 0.023$) and predominantly functional MR (odds ratio 4.714, 95% confidence interval: 1.105-20.112, $p = 0.036$) were independently related to acute postoperative improvement. In conclusion, immediately after TAVI, a significant improvement in MR is observed in two-thirds of patients undergoing TAVI and in an additional one-fifth at 12 months follow-up. Baseline EROA and predominantly functional MR pathology are associated with pre-discharge postoperative MR improvement.

INTRODUCTION

The prevalence of severe mitral regurgitation (MR) among patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) ranges between 1-9%.(1-4) Preoperative severe MR has been associated with poor short-term outcome after TAVI.(1-5) However, spontaneous reduction of MR after the procedure has also been demonstrated.(1,2,5-7) The time course of changes in MR after TAVI and the prognostic implications of these changes remain controversial.(1-3) Reasons for discrepant results may include non-systematic approach to quantify MR severity (semi-quantitative versus quantitative measurements), timing of assessment of MR after TAVI (short versus long-term follow-up) and underlying mechanism of MR (functional versus degenerative).

Time course characterization of changes in MR and investigation of the determinants of improvement in MR after TAVI may significantly aid the decision making of patients with severe aortic stenosis and concomitant significant MR. For patients in whom MR is expected to persist after TAVI the option of combined aortic and mitral valve surgery may need to be considered despite the increased surgical risk.(8,9) Alternatively, a combined TAVI and transcatheter mitral valve repair approach could be performed.(10,11) However, for patients with MR of borderline significance, the progression after TAVI is also ambiguous.(3) Hence, it is compelling to know which TAVI candidates will improve their MR after the procedure in order to optimize their selection for TAVI and overall management.

The present study evaluated changes in MR after TAVI in patients with symptomatic severe aortic stenosis and mild or more MR. The association between baseline clinical and echocardiographic parameters – including quantitative measurements of MR severity- and changes in MR was evaluated.

MATERIAL AND METHODS

From an ongoing registry of patients with symptomatic severe aortic stenosis and excessive risk or contraindications for cardiac surgery who were treated with TAVI,(12) 59 patients with concomitant mild or more MR were included in the present evaluation. Patients with mechanical mitral valves, mitral valve annuloplasty and bioprosthetic aortic valves, as well as patients with a valve-in-valve as a bailout procedure after TAVI were excluded.

Following institutional protocols, patients referred for TAVI underwent careful clinical evaluation and a comprehensive transthoracic echocardiographic analysis. After successful TAVI, patients underwent echocardiographic follow-up pre-TAVI, pre-discharge and at 12 months. Demographic, clinical and echocardiographic information were

prospectively collected in an electronic clinical file (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed. Changes in MR during follow-up were retrospectively examined and among various baseline clinical and echocardiographic parameters, independent correlates of post-TAVI MR improvement were investigated. The institutional review board approved the study and waived the need for patient written informed consent for retrospective analysis of clinically acquired data.

TAVI was performed in the catheterization laboratory under general anesthesia. The procedure was guided by fluoroscopy and additionally assisted by transesophageal echocardiography (iE33, Philips Medical System, Andover, MA, USA). Patients were treated with balloon-expandable (Edwards Sapien or Sapien XT, Edwards Lifescience, Irivine, CA) or self-expandable (CoreValve system, Medtronic, Minneapolis, MN) valves. Adequate valve sizing was based on multi-detector row computed tomography (MDCT) measurements of the aortic annulus. Coronary angiography was performed in all patients and percutaneous coronary interventions were performed when indicated. Transfemoral approach was applied in all patients treated with the CoreValve prosthesis. In patients treated with balloon-expandable valves, transfemoral approach was the first choice and the transapical approach was performed in cases where the anatomy of the ilio-femoral arteries was not considered suitable.(13) Under rapid right ventricular pacing, the native aortic valve was first dilated and thereafter, the balloon-expandable device was implanted. For the self-expandable prosthesis, rapid right ventricular pacing was not systematically performed. At this point, the post-procedural aortic regurgitation was assessed. In cases of significant paravalvular leak a post-dilatation of the implanted prosthesis was performed.

A commercially available ultrasound system (Vivid 7, E9, General Electric Horten, Norway) equipped with 3.5 MHz or M5S transducers was used to obtain transthoracic baseline and follow-up echocardiographic data. Quantification of left ventricular (LV) dimensions and function and calculation of LV mass were performed according to recommendations.(14) Furthermore LV end-diastolic (LVEDV) and end-systolic (LVESV) volumes were measured in the apical 4- and 2-chamber views and according to Simpson's method LV ejection fraction (LVEF) was derived.(14) The aortic valve morphology (bicuspid or tricuspid) was assessed in the parasternal short-axis view. The diameter of the LV outflow tract was measured in the parasternal long-axis view during mid-systole. Peak and mean transaortic pressure gradients were assessed in the apical long-axis and in the 5-chamber views. The aortic valve area was calculated with the continuity equation and the stenosis was considered severe if aortic valve area was <1.0 cm^2 and the transaortic mean gradient was ≥ 40 mmHg.(9) Systolic pulmonary arterial pressures were also calculated according to current guidelines.(15) Color-Doppler echocardiography was performed after optimization of the Nyquist limit and color gain settings. In order to diagnose and grade MR a multiparametric approach was used.(16) Effective

regurgitant orifice area (EROA) was calculated with the proximal isovelocity surface area (PISA) method.(16,17) In brief, the mitral valve was centered and zoomed at the apical 3- or 4-chamber view and the Nyquist limit was lowered to a point where the proximal flow convergence region could be clearly visualized. PISA radius was then measured in a mid-systolic frame. Peak velocity and time velocity integral of the mitral regurgitant jet were measured on continuous wave Doppler recordings of the mitral flow.(16,17) Regurgitant volume was calculated as the product of the surface area of the hemisphere and the velocity of aliasing.(16,17) The EROA was calculated from the ratio of regurgitant flow to peak regurgitant velocity. Vena contracta was additionally measured according to recommendations.(16,17)

The underlying mechanism of MR was defined as predominantly functional (when leaflets were non-pathologic) or degenerative (based on mitral leaflet prolapse, leaflet and chordae thickening and mitral annulus calcification).(18) Improvement of MR defined as reduction of the initial EROA by ≥30% (representing reduction by at least one grade) was evaluated before hospital discharge and at 12 months follow-up.(18)

SPSS software version 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Based on visual inspection of the histograms the continuous variables were categorized as normally distributed, and presented as mean and standard deviation or standard error of the mean, or non-normally distributed, and presented as median and inter-quartile range. Categorical variables were presented as frequencies and percentages.

Linear mixed model analysis was used to assess changes in mitral regurgitant volume, EROA, vena contracta, aortic valve area, transaortic mean gradient, LVEF, LV mass, LVEDV and LVESV and the mean and standard error of the mean were presented. Time (pre-TAVI, pre-discharge and 12 months) was used as the main fixed effect. The overall changes of each tested variable from baseline to follow-up and also between each specific time point were evaluated. Main effects were compared with Bonferroni adjustment.

Additionally, patients were categorized according to improvement (by ≥30% reduction of baseline EROA) or non-improvement of MR (<30% reduction of baseline EROA) during follow-up. Continuous variables were compared with the unpaired Student's t-test if they were normally distributed or the Mann-Whitney test otherwise. Categorical variables were compared with the χ^2 test or Fisher's exact test, as indicated. Binary logistic regression analysis was used for the evaluation of the associates of MR improvement and estimated odds ratios and 95% confidence intervals were calculated. On multivariate analysis only those variables with a $p < 0.2$ in the univariate model were included. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 and table 2 summarize the clinical and echocardiographic characteristics of the patients (mean age 82±6 years, male 41%). Patients had a mean logistic Euroscore I of 27±15%. Overall 56 (95%) Edwards Sapien valves (14 of 23 mm, 41 of 26 mm and 1 of 29 mm) and 3 (5%) CoreValve prostheses (2 of 26 mm, and 1 of 29 mm) were implanted. At baseline (pre-TAVI), mild MR was observed in 41 (70%) patients, moderate in 16 (27%), and severe in 2 (3%).

As expected, there was a significant overall increase in aortic valve area (from 0.70±0.02 cm^2 to pre-TAVI to 1.80±0.06 cm^2 pre-discharge and to 1.69±0.07 cm^2, $p < 0.001$ at 12 months follow-up), and reduction in transaortic mean gradient (from 38.7±2.0 mmHg to 9.9±0.6 mmHg and to 11.3±0.9 mmHg, $p < 0.001$) from baseline to pre-discharge to 12 months, respectively. In addition, significant reductions in LV mass (from 234±8 gr to 229±8 gr and to 215±7 gr, $p = 0.013$) and LVESV (from 71.9±5.9 ml to 68.6±5.3 ml and to 60.8±4.9 ml, $p = 0.042$) and an increase in LVEF (from 45.7±2.0% to 45.9±1.7% and to 50.5±1.5%, $p = 0.015$) were observed during the follow-up time. Changes in LVEF and LVESV were significant only between pre-discharge and 12 month

Table 1. Baseline characteristics of patients

	N = 59
Age (years)	82±6
Male n (%)	24(41)
BSA (m^2)	1.8±0.1
Creatinine (µmol/l)	95(76-156)
Diabetes mellitus n (%)	23(39)
Atrial fibrillation n (%)	17(29)
Peripheral vascular disease n (%)	29(49)
Smoking n (%)	22(37)
Coronary artery disease n (%)	42(71)
NYHA functional class III-IV n (%)	43(73)
Logistic Euroscore I (%)	27±15
Medications n (%)	
Beta-blockers	33(56)
Diuretics	48(81)
Statins	34(57)
Calcium antagonists	18(28)
ACE-inhibitors / ARB-II	32(54)
Transfemoral / Transapical TAVI n (%)	24(41)/35(59)
Edwards Sapien / CoreValve n (%)	56(95)/3(5)

ACE, Angiotensin converting enzyme; ARB-II, Angiotensin II receptor blocker; BSA, Body surface area; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation

Table 2. Baseline echocardiographic parameters

	N = 59
Aortic valve area (cm^2)	0.70±0.19
Mean transaortic gradient (mmHg)	39±16
Peak transaortic gradient (mmHg)	62±23
Left ventricular ejection fraction (%)	45±15
Left ventricular mass (gr)	234±67
Left ventricular end-diastolic volume (ml)	124 ±53
Left ventricular end-systolic volume (ml)	71±44
Systolic pulmonary arterial pressure (mmHg)	41±14
Left atrial volume index (ml/m^2)	44±14
Functional mitral regurgitation n (%)	17(29)
Mitral regurgitant volume (ml/beat)	35.6±7.1
Mitral EROA (mm^2)	20.5±8.4
Mitral vena contracta (mm)	5.0±1.2

EROA, Effective regurgitant orifice area

time points, indicating the occurrence of LV reverse remodeling at mid-term follow-up after TAVI (Table 3).

During the 12 months follow-up, there was an overall significant reduction in MR volume (from 35.6±2.2 ml to 18.0±1.8 ml and to 17.5±2.4 ml, $p < 0.001$), EROA (from 20.5±1.1 mm^2 to 13.9±1.2 mm^2 and to 10.6±1.2 mm^2, $p < 0.001$) and vena contracta (from 5.0±0.15 mm to 3.8±0.18 mm and to 3.5±0.24 mm, $p < 0.001$) (Table 3). Notably, for all MR parameters, changes were only significant between baseline and pre-discharge echocardiogram but not between pre-discharge and 12 months follow-up.

Table 3. Changes in mitral regurgitation, left ventricular dimensions and left ventricular function over a 12 month period following TAVI

	Pre-TAVI	**Pre-discharge**	**12-months Follow-up**	**p-value ***
Mitral regurgitant volume (ml)	35.6[2.2]	18.0 [1.8] †	17.5 [2.4] †	**<0.001**
Mitral EROA (mm^2)	20.5 [1.1]	13.9 [1.2]†	10.6 [1.2] †	**<0.001**
Mitral vena contracta (mm)	5.0 [0.15]	3.8 [0.18] †	3.5 [0.24] †	**<0.001**
AVA (cm^2)	0.70 [0.02]	1.80 [0.06] †	1.69 [0.07] †	**<0.001**
MG (mm Hg)	38.7 [2.0]	9.9 [0.6] †	11.3 [0.9] †	**<0.001**
LVEF (%)	45.7 [2.0]	45.9 [1.7]	50.5 [1.5] †	0.015
LV mass	234 [8]	229 [8]	215 [7] †	0.013
LVEDV (ml)	124.4 [6.9]	118.6 [6.1]	114.4 [6.4]	0.118
LVESV (ml)	71.9 [5.9]	68.6 [5.3]	60.8 [4.9] †	0.042

* p-values are given for total change of the parameter over the total follow up time.

† $p < 0.05$ vs. re-TAVI value.All values are expressed as mean [standard error of the mean].

AVA, Aortic valve Area; EROA, Effective regurgitant orifice area; LV, Left ventricle; LVEDV, LV end-diastolic volume; LVEF, LV ejection fraction; LVESV, LV end-systolic volume; MG, Mean Gradient.

Table 4. Comparison between MR improvers vs. MR non-improvers

Variables	MR improvers N = 35(59%)	MR non-improvers N = 24(41%)	p-value*
Age (years)	82±7	84±5	0.282
Male	13(37)	11(45)	0.504
Creatinine (μmol/l)	106(84-151)	90(69-124)	0.589
Diabetes	12(34)	11(45)	0.327
Atrial fibrillation	10(28)	7 (29)	0.960
Coronary artery disease	25(71)	17(70)	0.960
NYHA functional class III-IV	28(80)	15(62)	0.137
Logistic Euroscore I (%)	26±16	28±15	0.737
Transfemoral	16(45)	8(33)	0.342
Aortic valve area (cm^2)	0.70±0.18	0.70±0.20	0.946
Mean transaortic gradient (mmHg)	38±17	39±13	0.781
Peak transaortic gradient (mmHg)	62±24	62±20	0.965
Left ventricular ejection fraction (%)	45±14	47±17	0.708
Left ventricular mass (gr)	232±65	237±72	0.808
Left ventricular end-diastolic volume (ml)	126±48	121±61	0.753
Left ventricular end-systolic volume (ml)	74±42	68±50	0.647
Systolic pulmonary arterial pressure (mmHg)	40±14	43±15	0.539
Left atrial volume index (ml/m^2)	44±16	44±10	0.966
Mitral regurgitant volume (ml/beat)	37.5±17	32.8±17	0.305
Mitral EROA (mm^2)	22.8±8.8	17.3±7.5	**0.013**
Mitral vena contracta (mm)	5.2±1.2	4.8±1.1	0.188
Functional mitral regurgitation	14(40)	3(12)	**0.022**

*p-values are given for the difference in baseline characteristics between patients with a reduction in effective regurgitant orifice area by ≥30% after TAVI (MR improvers) vs. patients with <30% reduction (MR non-improvers). EROA, Effective regurgitant orifice area; MR, Mitral regurgitation; NYHA: New York Heart Association.

Overall, MR improved by ≥30% reduction in EROA at pre-discharge in 35 (59%) patients whereas in 24(41%) EROA reduced by <30%, remained unchanged or worsened. At 12 months follow-up MR improved by ≥30% reduction of baseline EROA in an additional 10 (17%) patients in whom an acute post-TAVI improvement had not been observed. There were no differences between acute improvers and non-improvers in logistic Euroscore (26±16% vs. 28±15%, p = 0.737), baseline aortic valve area (0.70±0.18 cm^2 vs. 0.70±0.20 cm^2, p = 0.946) or mean aortic valve gradient (38±17 mmHg vs. 39±13 mmHg, p = 0.781). LV volumes and LVEF similarly did not differ between groups (Table 4). However, patients with acute improvement in MR after TAVI had higher baseline EROA compared to non-improvers (22.8±8.8 mm^2 vs. 17.3±7.5 mm^2, p = 0.013). In addition, the proportion of predominantly functional MR was higher among the MR improvers than non-improvers (14 (40%) vs. 3 (12%), respectively; p = 0.022) (Table 4).

Table 5. Correlates of postoperative reduction in EROA area by ≥30% of baseline EROA following TAVI

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (years)	0.955 (0.897-1.038)	0.280		
Male	0.698 (0.678-2.007)	0.231		
Creatinine (μmol/l)	0.997 (0.989-1.004)	0.343		
Diabetes	0.617 (0.213-1.787)	0.373		
Atrial fibrillation	0.971 (0.309-3.055)	0.960		
Coronary artery disease	0.960 (0.327-3.237)	0.961		
Aortic valve area (cm^2)	0.907 (0.058-14.616)	0.907		
Mean transaortic gradient (mmHg)	0.995 (0.963-1.029)	0.777		
Left ventricular ejection fraction (%)	0.993 (0.960-1.028)	0.703		
Left ventricular mass (gr)	0.999 (0.991-1.007)	0.804		
Left ventricular end-diastolic volume (ml)	1.002 (0.992-1.012)	0.748		
Left ventricular end-systolic volume (ml)	1.003 (0.991-1.014)	0.668		
Systolic pulmonary pressure (mmHg)	0.988 (0.953-1.025)	0.532		
Left atrial volume indexed (ml/m^2)	0.999 (0.963-1.037)	0.965		
Mitral EROA (mm^2)	1.093 (1.015-1.177)	**0.019**	1.095 (1.013-1.185)	**0.023**
Functional mitral regurgitation	4.667 (1.167-18.659)	**0.029**	4.714 (1.105-20.112)	**0.036**

CI, confidence interval; EROA, Effective regurgitant orifice area; OR, odds ratio

In the univariate analysis only baseline EROA (odds ratio 1.093, 95% confidence interval: 1.015-1.177, p = 0.019) and functional MR (odds ratio 4.667, 95% confidence interval: 1.167-18.659, p = 0.029) were associated with post-TAVI MR improvement. Both baseline mitral EROA (odds ratio 1.095, 95% confidence interval: 1.013-1.185, p = 0.023) and functional MR (odds ratio 4.714, 95% confidence interval: 1.105-20.112, p = 0.036) were independently related to post-TAVI MR improvement (Table 5).

DISCUSSION

The present evaluation showed that in patients with severe aortic stenosis and concomitant mild or more MR who are treated with TAVI, a significant improvement in MR (defined by ≥30% reduction of baseline EROA) occurs in 59% of patients immediately after TAVI and in an additional 17% at 12 months follow-up. In addition, significant reductions in LV volumes and improvement in LVEF were observed at 12 months follow-up. Baseline EROA and predominantly functional MR were independently associated with acute improvement in MR. These findings indicate that the acute improvement in MR is driven by a significant reduction in LV pressure afterload and in systolic left-atrium-LV pressure gradient whereas the MR improvement at mid-term follow-up may be associated with LV reverse remodeling.

Although patients with significant MR were generally excluded from early TAVI studies, data from registries report a prevalence of 1-9% of severe MR among TAVI recipients while the percentage of patients with at least moderate MR ranges between 24-48%.(1-3,5) Differences in reported MR prevalence may be related to a non-standardized assessment of MR grade. Only a few series have used quantitative measurements of MR severity in patients undergoing TAVI.(6,7) For example, Giordana et al reported a mean EROA of 24.4±11.5 mm^2 in 35 patients treated with TAVI.(6) In addition, data from the TRanscatheter EndoVascular Implantation of VALves (REVIVAL) II trial showed that 63% of patients had at least mild-moderate MR with a mean vena contracta width of 0.5±0.2 cm.(7) Quantification of MR prior to aortic valve replacement is relevant since the presence of more than moderate MR may indicate a double valve replacement.(9) However, several series have shown that MR may improve after aortic valve replacement, which coincides with better long-term outcome.(4,19)

Quantitative evaluation of changes in MR and timing of these changes are also important for decision making of patients with severe aortic stenosis. The present study showed that the majority of patients improved by ≥30% reduction in EROA immediately after TAVI and only one-fifth improve later at follow-up in parallel with timing of manifest LV reverse remodeling. The Placement of Aortic Transcatheter Valve (PARTNER) trial cohort A showed an improvement by ≥1 grade at 30 days in 57.7% of patients with at least moderate MR at baseline who were treated with TAVI.(19) However, the prevalence of moderate and severe MR remained unchanged at 1 year follow-up (17% at 30 days vs 19.9% at 1 year).(20) Of note, for overall patients allocated to the TAVI arm, there was a significant reduction in MR grade at 2 years follow-up (from 1.94 ± 0.78 at baseline to 1.65 ± 0.84 at discharge and 1.67 ± 0.81 at 2 years; $p = 0.03$) together with reductions in LVESV (from 57.9 ± 35.1 ml at baseline to 52.8 ± 30.9 ml at discharge and 50.9 ± 29.5 ml at 2 years, $p = 0.04$) and improvement in LVEF (from 53.4 ± 12.6% at baseline to 53.8 ± 12.1% at discharge and 57.4 ± 10.4% at 2 years, $p < 0.001$).(20) These results confirm our findings and indicate that there is a significant reduction in MR acutely, probably due to reductions in LV pressure overload and pressure between left atrium and LV, and a further improvement at mid- and long-term follow-up related most likely to changes in LV volumes and improvement in LVEF. However, it remains unclear how to identify the patients who will show an improvement in MR after aortic valve replacement and the patients who may benefit from double valve replacement.

Several studies have evaluated the determinants of improvement in MR after aortic valve replacement.(21-28) The largest evidence is based on surgical aortic valve replacement trials. The results are disparate, probably due to different methodologies to quantify MR severity and heterogeneous populations. However, a few factors are frequently observed: functional MR and MR grade at baseline are associated with improvement in MR after aortic valve replacement.(22-26) In patients undergoing TAVI,

few studies have investigated the associates of improvement in MR after TAVI.(1,2,4,9) For example, Toggweiler et al showed that the presence of functional MR was associated with increased probability of improvement in MR at 1 year follow-up after TAVI. (1) Similarly, data from the Italian registry showed that independent associates of MR improvement after TAVI were functional etiology of MR (OR 2.6, p = 0.005), absence of atrial fibrillation (OR 2.02, p = 0.003) and absence of pulmonary hypertension (OR 2.9 p = 0.002).(4) From the PARTNER trial cohort A, LV end-diastolic diameter was a univariate associate of improvement in MR (OR 5.42, p = 0.02).(19) However, independent factors associated with MR improvement were not observed. Similarly, the present study showed that functional MR and larger baseline EROA were independently associated with improvement in MR after TAVI. In contrast to organic etiology of MR, functional MR may respond to an acute reduction in LV pressure overload. Reduction in EROA to define improvement in MR is a rather strong parameter, since EROA is less load dependent than other parameters such as regurgitant volume or color flow mapping. A reduction in ≥30% of baseline EROA may only be observed in patients with a large baseline EROA. Therefore, it is not surprising that this parameter is independently associated with MR improvement.

There are some notable clinical implications of this evaluation. Reduction in MR after TAVI is occurring mainly at pre-hospital discharge and there may not be a reason for delaying an additional intervention when MR persists after TAVI. In addition, patients with significant MR may not be excluded from TAVI, especially if the underlying MR pathology is functional. On the other hand, for TAVI candidates with significant MR of predominantly degenerative pathology, surgical aortic valve replacement or staged transcatheter mitral valve repair may be considered.

Several limitations of this study should be acknowledged. The study was retrospective and performed in a single center. The number of patients with severe MR at baseline was relatively low. Moreover, for the initial inclusion of patients a semi-quantitative approach of MR grading was performed. The follow-up echocardiogram was available only for 44 of the 59 initially included patients. Finally, only 3 patients with CoreValve system were included and the influence of the type of prosthesis in postoperative MR cannot be appraised.

CONCLUSION

In patients with more than mild MR undergoing TAVI there is a significant MR reduction in the acute post-operative phase in almost two-thirds of patients. However, an additional 17% of patients may show a later mid-term improvement. Baseline mitral EROA and predominately functional MR are independently related to acute MR improvement.

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Chapter 8

Fate of transcatheter valve-in-valve implantation and redo cardiac surgery for failing bioprosthetic valves in patients with high operative risk

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Submitted

ABSTRACT

Objectives: The aim of the present evaluation was to compare the clinical outcome of patients with failing cardiac bioprostheses or mitral valve annuloplasty treated with transcatheter valve-in-valve with patients who underwent redo cardiac surgery.**Background:** Transcatheter valve-in-valve implantation is a feasible treatment for patients with failing degenerated cardiac bioprostheses with increased operative risk, however the outcome of this therapy has not been compared with redo cardiac surgery. **Methods:** The long-term survival of 16 patients (age 80±2. 25% male) undergoing transcatheter valve-in-valve procedure was compared with that of 16 high-operative risk patients (age 70±1, 50% male) undergoing redo valve surgery. **Results:** Both groups of patients were comparable in terms of preoperative risk (logistic Euroscore I: 34.1±14.6% in patients treated with valve-in-valve vs. 30.8±20.3% in patients treated with redo surgery p = 0.605), functional status (New York Heart Association class ≥III: 9 (56%) in patients treated with valve-in-valve vs. 7(44%) in patients treated with redo surgery, p = 1.000) and left ventricular ejection fraction (37% (27-52) in patients treated with valve-in-valve vs. 40% (26-57) in patients treated with redo surgery, p = 0.724). After a median follow-up of 21 months (interquartile range 7-44), 10 (30%) patients died. Survival for patients treated with valve-in-valve did not differ from that of patients treated with redo cardiac surgery (log-rank p = 0.939).**Conclusions:** Patients with failing cardiac bioprostheses and high operative risk treated with transcatheter valve-in-valve have similar survival compared with patients undergoing redo cardiac surgery.

INTRODUCTION

Structural valve deterioration is one of the main complications associated with bioprosthetic heart valves. Landmark randomized trials have shown a greater incidence of prosthetic heart valve failure among patients aged <65 years receiving aortic or mitral bioprostheses as compared with recipients of a mechanical prosthesis.(1-2) The incidence of structural valve deterioration declines significantly among patients older than 65 years. In large registries including more than 300, 000 patients undergoing aortic valve replacement the reoperation rate for patients receiving a bioprosthesis was 3.1% at 11-13 years of follow-up compared with 2.3% reoperation rate for recipients of an aortic mechanical prosthesis.(3) However, the lower reoperation rates of mechanical valve prostheses are counterbalanced by an increased risk of bleeding complications associated with the lifelong use of anticoagulation.(1-3) This has resulted in a significant increase of bioprostheses over the last decades (from 18% in 1991 to 59% in 2003), mainly among older patients with associated comorbidities.(3) These patients who may present at follow-up with failing degenerated bioprostheses have an increased risk for reoperation.

The development of transcatheter aortic valve devices and the promising results of transcatheter aortic valve implantation in patients with high operative risk or who are deemed inoperable, has led to the off-label use of these devices in other high risk subgroups such as patients with failing degenerated cardiac bioprostheses.(4-6) Dvir et al have recently reported the outcomes of 202 patients with failing aortic bioprostheses who underwent transcatheter valve-in-valve implantation, the largest series described so far. (4) The procedural success rate was 93.1% and the 1-year survival (based on data available from 85 patients) was almost 86%. (4) However, the results of this series concerned only patients with failing degenerated aortic bioprostheses and were not compared with a control group of patients undergoing redo cardiac valve surgery. The outcome of transcatheter valve-in-valve implantation in positions other than aortic (mitral or tricuspid) or in failing mitral annuloplasty was not evaluated. Accordingly, the aim of the present evaluation was to compare the clinical outcome of patients with failing cardiac bioprostheses or mitral valve annuloplasty treated with transcatheter valve-in-valve with high risk patients who underwent redo cardiac surgery.

MATERIALS AND METHODS

The present evaluation included patients who underwent elective transcatheter valve-in-valve procedures or redo cardiac surgery for failing aortic or mitral bioprostheses or failing mitral valve annuloplasty. From February 2008, transcatheter valve-in-valve has been a therapeutic alternative to cardiac surgery at our institution for patients with

failing degenerated aortic or mitral bioprostheses and very high operative risk or contraindications for surgery. In addition, from 2010 this therapy was extended to patients with failing mitral valve annuloplasty and contraindications for surgery. All patients provided informed consent for the procedures. The clinical and echocardiographic data of this population were prospectively collected in the departmental Cardiology Information System (EPD-Vision®, Leiden University Medical Centre) and retrospectively analysed.

Furthermore, a retrospective search in the echocardiographic database was performed to identify patients who underwent elective redo cardiac surgery for failing mitral and aortic (biological or mechanical) prostheses and failing mitral valve annuloplasty. Patients with active endocarditis were excluded. The clinical characteristics and logistic Euroscore I in this group were reviewed to further select a similar comparator group of patients treated with transcatheter valve-in-valve.

The long-term outcome of patients undergoing transcatheter valve-in-valve and patients undergoing redo cardiac surgery were compared. All cause-mortality was the primary endpoint. The institutional review board approved the retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Clinical and echocardiographic data

Clinical data, including demographics, comorbidities, logistic Euroscore I and medications were recorded. All patients underwent transthoracic and transesophageal echocardiography prior to the procedures. Left ventricular (LV) end-diastolic (LVEDV) and end-systolic volumes (LVESV) were measured using the Simpson method and LV ejection fraction (LVEF) was derived.(7) Type of valvular prosthesis dysfunction (regurgitation or stenosis) and its severity were evaluated according to current recommendations.(8)

Transcatheter valve-in-valve procedure

Transcatheter valve-in-valve procedures were performed at the hybrid operating room, under general anesthesia and with fluoroscopy and transesophageal echocardiography guidance. Edwards Sapien or Sapien XT valves were implanted in aortic or mitral positions through a transapical approach to allow a proper coaxial alignment of the transcatheter valve within the prosthetic valve [5]. For valve-in-ring procedures, the transcatheter valve was positioned at the center of the mitral valve with 50% of the frame in the left atrium and 50% in the left ventricle.(9)

Follow-up

Following one month after the procedure a repeat comprehensive echocardiographic study was performed for patients treated with transcatheter valve-in-valve. LVEDV, LVESV and LVEF and the hemodynamics of the valve were assessed. (7-8) In addition, patients were prospectively followed-up for all-cause mortality.

For patients treated with redo cardiac surgery, data on all-cause mortality was collected by retrospective review of medical records and retrieval of survival status through the municipal civil registries.

Statistical analysis

A package of SPSS software version 20, (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The Gaussian distribution of continuous variables was checked with the Kolmogorov-Smirnov test. If normally distributed, continuous variables were presented as mean and standard deviation. Otherwise, median and interquartile range was provided. Categorical variables were presented as number and frequencies. The Student's t-test or Mann-Whitney test were used to compare continuous variables normally or non-normally distributed, respectively. Categorical variables were compared with the χ^2 test or Fisher's exact test, as appropriate. Patients were dichotomized according to treatment with redo cardiac surgery or transcatheter valve-in-valve procedure. Cumulative events rates were calculated using the Kaplan-Meier method and were then compared across groups with the log-rank test.

RESULTS

Preoperative clinical and echocardiography characteristics

The population consisted of 32 patients with failing mitral or aortic prostheses or failing mitral valve annuloplasty: 16 patients treated with transcatheter valve-in-valve procedure between September 2008 and April 2012 (Table 1) and 16 who underwent redo cardiac surgery between June 2000 and February 2008 (Table 2). In the group of patients undergoing transcatheter valve-in-valve, the mechanism of prosthesis failure was severe aortic stenosis in 7 patients, severe aortic regurgitation in 3, and combined aortic stenosis and regurgitation in 2. The remaining 4 patients had severe mitral regurgitation. In the group of patients who underwent redo cardiac valve surgery, aortic stenosis was observed in 4 patients, aortic regurgitation in 7 and combined aortic stenosis and regurgitation in 4. Moreover, one patient had combined stenosis and regurgitation of the degenerative aortic bioprosthesis and severe regurgitation of the native mitral valve and was treated with surgical replacement of both valves.

Table 3 summarizes the baseline characteristics of the overall population and both groups of patients. Patients treated with transcatheter valve-in-valve were significantly older than patients treated with redo cardiac surgery (80±2 vs. 70±1 years, respectively; $p = 0.001$). However, there were no differences in logistic Euroscore I or comorbidities, such as diabetes, renal dysfunction, and clinical symptoms (Table 3). Additionally, LVEF was comparable in both groups (37(27-52)% in patients treated

Table 1. Brief history of patients undergoing transcatheter valve-in-valve procedures

Patient no	Previous cardiac surgery	Type of failure	Age	Log Euroscore I	Transcatheter valve-in-valve
1	AVR (Medronic Freestyle stentless 21 mm)	AS	62	16.45	AV Edwards Sapien 23 mm
2	AVR (Carpentier Edwards bioprosthesis 21 mm) + MVP	AS	78	17.05	AV Edwards Sapien 23 mm
3	AVR (Medronic Freestyle 23 mm)	AR	84	18.06	AV Edwards Sapien 26 mm
4	AVR (Medronic Freestyle 23 mm)	AS	85	24.69	AV Edwards Sapien 23 mm
5	AVR + MVP (Edwards annuloplasty ring 28 mm) + CABG	MR	74	25.58	MV Edwards Sapien 26 mm
6	AVR (Carpentier Edwards 23 mm)	AS	77	26.29	AV Edwards Sapien 23 mm
7	AVR (Carpentier Edwards 21 mm) + CABG	AS	89	29.97	AV Edwards Sapien 23 mm
8	AVR (Carpentier Edwards Perimount bioprosthesis 23 mm) + MVP + TVP + GABG	AS	83	30.38	AV Edwards Sapien 23 mm
9	AVR (Medronic Mosaic bioprosthesis 23 mm) + CABG + MVP + TVP	AS	72	31.39	AV Edwards Sapien 23 mm
10	MVR (Medronic Intact bioproshesis 27 mm)	MR	82	33.24	MV Edwards Sapien 26 mm
11	AVR + MVR (Medronic Mosaic bioprosthesis 27 mm)	MR	79	41.83	MV Edwards Sapien 26 mm
12	AVR (Carpentier Edwards 25 mm) + CABG	AR	91	51.44	AV Edwards Sapien 26 mm
13	AVR (Medronic Freestyle 23 mm) + CAGB	AR	82	52.61	AV Edwards Sapien 26 mm
14	AVR (Medronic Intact 25 mm) + CABG	AS+AR	83	58.39	AV Edwards Sapien 26 mm
15	AVR (Medronic Freestyle 23 mm)	AS+AR	81	61.78	AV Edwards Sapien 26 mm
16	MVP (Edwards annuloplasty ring 28 mm) + TVP	MR	81	27.62	MV Edwards Sapien 26 mm

Data are expressed as number, AS, aortic stenosis; AR, aortic regurgitation; AVR, aortic valve replacement; CABG, Coronary artery bypass grafting, MR, mitral regurgitation; MVP, Mitral valve repair; MVR, Mitral valve replacement; TVP, tricuspid valve annuloplasty

with transcatheter valve-in-valve vs. 40 (26-57)% in patients undergoing redo cardiac surgery, p = 0.724).

Echocardiographic follow-up of patients undergoing transcatheter valve-in-valve procedures

In the group of patients undergoing transcatheter valve-in-valve in aortic position, LVEF increased at 1 month follow-up (37% (28-48) vs. 40% (26-53), p = 0.014) and the peak and mean transvalvular gradients were 30.5 (23.7-45.5) mmHg and 16 (10.2-20) mmHg, respectively. Severe intra-valvular regurgitation immediately after deployment of the transcatheter valve into the prosthetic aortic valve requiring emergent repeat transcatheter valve-in-valve was recorded in one patient.(10) Mild paravalvular regurgitation was observed in 1 (10%) patient at follow-up. In patients treated with transcatheter valve-in-

Table 2. Brief history of patients undergoing redo cardiac surgery

Patient no	Previous cardiac surgery	Type of failure	Age	Log Euroscore I	Redo cardiac surgery
17	AVR(Medtronic Intact 23 mm)	AS+AR	81	83.75	AVR(Edwards Lifesciences 23 mm) + CABG
18	AVR (Medtronic Hall 29 mm)	AR	62	13.77	AVR (St. Jude Medical 29 mm)
19	MVR (Medronic Intact bioproshesis 33 mm)	AR	76	17.87	AVR (Edwards pericardial 23 mm) + MVP
20	AVR (NA)	AR	65	20.19	AVR (Medtronic Freestyle 29 mm)
21	AVR (Carpentier Edwards 23 mm)	AS	81	20.33	AVR(Hancock II porcine Medtronic 23 mm) + MVR (Edwards 29 mm)
22	AVR(Medtronic Freestyle 27 mm)	AS+AR	59	22.64	AVR (St. Jude Medical 29 mm)
23	MVR (Carbomedics 29 mm)	AS	71	24.68	AVR (Carbomedics 21 mm) + MVP+TVP
24	AVR (St. Jude Medical 25 mm)	AR	65	35.72	AVR (Carpentier-Edwards Perimount magna 25 mm) + CAGB
25	AVR (Medronic Hall Mechanical 23 mm)	AS+AR	69	35.80	AVR (Carpentier-Edwards Perimount 23 mm)
26	AVR (Medronic Mosaic ultra 27 mm)	AR	71	14.67	AVR (Medronic Mosaic ultra 27 mm)
27	AVR (Carpentier-Edwards Perimount 21 mm)	AS+AR+ MR	66	23.07	AVR (St. Jude Medical 23 mm) + MVR (St. Jude Medical 31 mm) + CABG
28	AVR (Bjork-Shilley 25 mm)	AR	52	69.11	AVR (St. Jude Toronto stentless 29 mm) + Hemashield prosthesis32 mm
29	AVR (Carbomedics 25 mm)	AR	68	46.49	AVR (Medtronic Freestyle 29 mm) + MVP + TVP
30	AVR (Medronic Mosaic 19 mm)	AS	76	16.03	AVR (Medtronic Freestyle 23 mm)
31	AVR (Medronic Intact 25 mm)	AS	84	23.42	AVR (Edwards Perimount Magna 23 mm)
32	AVR (Medtronic Freestyle 27 mm)	AS+AR	76	33.14	AVR (Edwards Perimount Magna 25 mm)

Data are expressed as number, AS, aortic stenosis; AR, aortic regurgitation; AVR, aortic valve replacement; CABG, Coronary artery bypass grafting; MR, mitral regurgitation; MVP, Mitral valve repair; MVR, Mitral valve replacement; TVP, tricuspid valve annuloplasty.

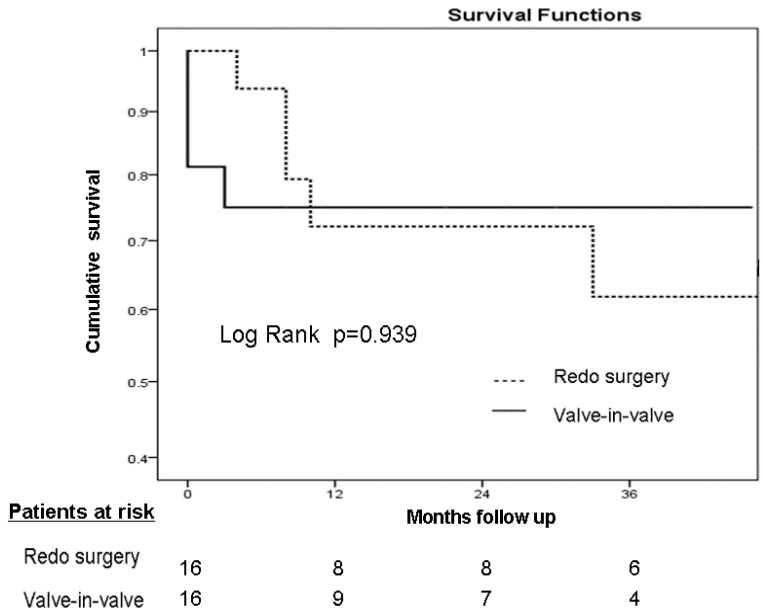
valve for failing mitral valve bioprosthesis the peak and mean transvalvular gradients at 1 month follow-up were 13.4 mmHg and 5 mmHg, respectively. Finally, only one of the 2 patients treated with transcatheter valve-in-ring survived at 1 month follow-up and underwent repeat echocardiography. The peak and mean transvalvular gradient were 17 and 6.5 mmHg, respectively.

Table 3. Baseline characteristics of population

Variable	Overall (n = 32)	REDO surgery (n = 16)	Valve-in-valve (n = 16)	p-value
Age (years)	75±9	70±1	80±2	**0.001**
Male, n (%)	12(38%)	8(50%)	4(25%)	0.273
Diabetes, n (%)	3 (13%)	1(6%)	3(19%)	0.600
Creatinine (µmol/L)	94 (73-140)	94 (73-167)	94 (67-140)	0.879
Coronary artery disease, n (%)	14 (44%)	4(25%)	10(63%)	0.073
NYHA functional class III-IV, n (%)	15 (47%)	7(44%)	8(50%)	1.000
Atrial Fibrilation, n (%)	16 (50%)	7(44%)	9 (56%)	0.724
Medication, n (%)				
Beta-blockers	14 (44%)	8(50%)	6(38%)	0.722
Diuretics	25(78%)	13(81%)	12(75%)	0.669
Statins	14 (44%)	8(50%)	6(38%)	0.722
ACE inhibitors	20(63%)	9(56%)	11(69%)	0.716
Logistic Euroscore I	32.5±17.5	30.8±20.3	34.1±14.6	0.605
Left ventricular ejection fraction (%)	38(27-55)	40(26-57)	37(27-52)	0.724
Years since previous cardiac surgery	9±5	9±6	9±4	0.696
Number of previous cardiac surgeries	1(1-2)	1(1-1)	1(1-3)	0.423

Data are expressed as n (%), mean ± SD and median (interquartile range), ACE, Angiotensin converting enzyme; NYHA, New York Heart Association. p Value (REDO surgery vs Valve-in-Valve)

Figure 1. Kaplan-Meier method for comparison between patients treated with surgical redo or transcatheter valve-in-valve with Edwards Sapien valve for failing bioprosthetic valves.



Outcomes

In the group treated with transcatheter valve-in-valve, 2 patients died before hospital discharge (in-hospital mortality 12%) whereas in the surgically treated group there were no in-hospital deaths. During a median follow-up of 21 (7-41) months, 10 (30%) patients died. Cumulative survival at 12 and 24 months for the group of patients treated with valve-in-valve procedure were 75% and 75%, respectively, whereas for the redo cardiac surgery group the survival rates were 72% and 72%, respectively (log-rank, $p = 0.939$) (Figure 1).

DISCUSSION

The present single center experience shows that the long-term survival of patients with failing bioprosthetic valves and high operative risk who underwent transcatheter valve-in-valve implantation is similar to that of high risk patients who were treated with redo cardiac surgery.

The choice of a mechanical or a biological prosthesis is mainly determined by the risks associated with lifelong anticoagulant treatment for mechanical prostheses (bleeding and thromboembolism) and the risk of structural valve degeneration of biological prostheses. These risks are strongly associated with age and comorbidities of the patients and valve position (mitral vs. aortic). In the Veterans Affairs trial, randomizing 575 patients to mechanical or biological prosthesis in aortic or mitral positions, an increased structural deterioration of bioprosthetic valves was observed only for patients younger than 65 years.(1) In addition, the Edinburgh Heart Valve trial, randomizing 541 patients to mechanical prosthesis (Bjork-Shiley) or porcine prostheses (Hancock or Carpentier-Edwards), reported a lower 20-year reoperation rate among patients receiving a mechanical prosthesis than recipients of a porcine prosthesis (2.5% vs. 5%, $p < 0.001$).(2) However, the differences were more pronounced after 8-10 years for mitral valve prostheses and after 12-14 years for aortic valve prostheses. Therefore, current guidelines recommend the use of bioprosthetic valves only for patients ≥65 years of age.(11) At the same time, real life evidence shows that bioprosthetic valves are gradually prevailing over mechanical valves, given the avoidance of need for anticoagulation and its associated lifetime bleeding risk.(11-12) A more recent observational study including more than 300,000 patients older than 65 years undergoing aortic valve replacement confirmed the increased risk of reoperation associated with the use of bioprostheses.(3) However, the study reported an increase in the use of bioprostheses over time (from 18% in 1991 to 59% in 2003). Interestingly, patients receiving an aortic bioprosthesis were more likely to have associated comorbidities such as diabetes, chronic heart failure, renal dysfunction, cerebrovascular disease and chronic obstructive pulmonary disease that contribute to an increased surgical risk of a redo cardiac surgery in the future.(3,13-16)

In recent years, the number of transcatheter valve-in-valve procedures has increased considerably. Reports from pioneer centers have shown acceptable inhospital survival for patients with failing bioprosthetic valves treated with transcatheter valve-in-valve procedures.(5,17-21) Still, most reports include small numbers of patients with limited follow-up time and concern almost exclusively degenerated aortic bioprostheses. Recently, the Global valve-in-valve registry of 202 patients showed that the 30-day-mortality (8.4%) and one year survival (85.8%) of patients treated with valve-in-valve procedure did not differ significantly from survival observed in large transcatheter aortic valve implantation trials. (22) However, this registry included exclusively patients with failing bioprosthetic aortic valves and did not include a control group of patients treated with redo cardiac surgery.

The present study includes patients with both failing aortic and mitral bioprosthetic valves and additionally attempts to compare their long-term survival with a group of patients with similar preoperative risk that were treated surgically. Logistic Euroscore I was similar between groups. Patient groups were also comparable for other clinical characteristics that determine the outcome of redo cardiac valve surgery such as elective surgery, (13) renal dysfunction, (23) New York Heart Association functional class (13,15,16) and LVEF. (13,14) Survival after transcatheter valve-in-valve procedure was comparable to that of redo cardiac surgery suggesting that this technique could be an alternative for high risk patients in need of bioprosthesis valve replacement.

Transcatheter valve-in-valve offers many advantages compared to cardiac surgery. It is minimally invasive and technically simpler because sternotomy and cardiopulmonary bypass are not required. The increased awareness of this option alongside further studies demonstrating its feasibility will likely lead to growing numbers of patient referrals for transcatheter valve-in-valve procedures in the near future. Specifically, elderly patients at very high surgical risk who may have been previously deemed inoperable will have a potential alternative and viable option. Moreover the increasing use of bioprosthetic over mechanical valves that has already been observed in larger registries may be further extended.(12) Finally, in everyday practice, it will be important for surgeons to use larger aortic bioprostheses and adapt their surgical technique in order to make a valve-in-valve reoperation more feasible. (6)

LIMITATIONS

There are some limitations of this study. This is a report from a single center, with a small number of patients that are not matched one by one for preoperative risk parameters. Moreover the follow-up of the redo surgical group was assessed retrospectively. These results need to be confirmed in larger series of patients and possibly in randomized trials.

CONCLUSIONS

This study indicates that high risk patients with degenerated bioprosthetic valves treated with transcatheter valve-in-valve implantation have similar long term survival with an analogous group treated with redo cardiac valve surgery. Therefore, transcatheter valve-in-valve is a feasible alternative for high risk patients with degenerated bioprosthetic valves. These results need to be confirmed in larger series of patients and possibly in randomized trials.

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Summary and Conclusions

The introduction of the thesis provided an overview of the role of transcatheter aortic valve implantation (TAVI) in current clinical practice with special focus on paravalvular aortic regurgitation (AR) and conduction disturbances. Also, detailed information were provided concerning the clinical role of multi-detector computed tomography (MDCT) to assist procedure planning and clarify the pathophysiology of procedural complications. There was additionally an overview of the so called "off-label" transcatheter aortic valve treatment for patients with failing bioprostheses and contraindications for conventional surgical treatment. Minimizing procedural complications and understanding the challenges of widening current TAVI indications may help us to optimize the outcome of patients referred for TAVI.

PART I

This part of the thesis focused on role of MDCT to improve the management of patients undergoing TAVI. Clinical and demographical data in combination with information from the analysis of pre-operative and post-operative MDCT scans of patients undergoing TAVI, were correlated with procedural complications. In **Chapter 2** we sought the relation of the deployment of the Edwards SAPIEN frame in the aortic root and the presence of postprocedural paravalvular AR. Amongst various clinical and MDCT derived parameters, the difference between the MDCT derived maximum annulus diameter and the nominal diameter of the prosthesis and shallow position of the frame in the left ventricular outflow tract (LVOT) were independently related to significant paravalvular AR. These results underscore the association of prosthesis undersizing with paravalvular AR. In addition, a shallow position of the Edwards SAPIEN valve into the LVOT may lead to suboptimal cover area by the skirt of the frame, leading to paravalvular AR. Combination of pre- and post-implant MDCT was also used to define the pathophysiology of major conduction disorders following TAVI in **Chapter 3**. Amongst several anatomical, electrophysiological, MDCT and procedural parameters, implantation depth of the frame in the LVOT and overexpanding of the frame by >15% of the native aortic annulus area (measured on MDCT) were independently related with the need of pacemaker or new-onset LBBB. These results may be pathophysiologically explained by a deep implantation of the frame that may damage the atrio-ventricular node or left bundle branch while overexpansion of the frame can also induce compression forces into the left ventricular outflow tract. The clarification of the mechanisms responsible for new onset conduction disorders may have an impact on procedural planning and may also help the design of future transcatheter aortic valves. The clinical implications of positioning of the frame into the aortic root were further investigated with post-TAVI MDCT in **Chapter 4**. Specifically, the relation of the expanded frame with the ostia was

systematically investigated in 142 patients. Interestingly in 7.7% of patients there was a full overlap of the frame with any of the coronary ostia and in 35.9% of cases the frame overlapped the coronary ostia by >3 mm. Partly or full overlap of the coronary ostia by the frame was not related to post-operative troponin leak or to long-term occurrence and feasibility of new percutaneous coronary intervention. We have also shown that impingement of the coronary ostia by the frame is relatively rare and may be not systematically related to perioperative ischemia. **Chapter 5** discusses the occurrence of early and late pericardial effusion after TAVI, a complication that remains barely evaluated. New onset moderate pericardial effusion at 1 month after the procedure was diagnosed with echocardiography and MDCT in 2.5% of patients and only in cases treated with transapical TAVI. However, there were no documented clinical signs or symptoms of cardiac tamponate in any of the patients. It should be emphasised that there were some discrepancies in pericardial effusion grading between imaging modalities. The clinical significance of these findings is not clear.

PART II

This part of the thesis focuses on the outcome of specific populations of patients undergoing TAVI. Particularly, **Chapter 6** discusses the outcome of patients with high baseline valvulo-arterial impedance (ZVa), an echocardiographic derived marker of global (valvular and arterial) afterload in aortic stenosis patients. Patients with baseline ZVa ≥5 mmHg/mL/m^2 had higher mortality rates compared to patients with lower ZVa values. Moreover baseline ZVa was independently associated with all-cause mortality at follow-up. A higher baseline ZVa levels may be associated with advanced myocardial fibrosis and dysfunction. This measurement could be implemented in future TAVI risk scores, optimizing selection of patients that may benefit from the procedure. In **Chapter 7** there is a special focus on patients with significant mitral regurgitation undergoing TAVI. Severe mitral regurgitation is generally considered contraindication for TAVI. However, patients with severe aortic stenosis and concomitant significant mitral regurgitation deemed inoperable or at excessive surgical risk may still undergo TAVI as a last bailout treatment. Patients with mild or more mitral regurgitation were included and quantitative analysis of mitral regurgitation evaluation was performed at baseline, pre-discharge and 12 months follow-up echocardiography. There was a significant acute post-operative reduction of mitral regurgitation in the overall population. Baseline effective orifice area and predominantly functional mitral regurgitation were independently related to acute pre-discharge improvement. These results underscore that TAVI candidates with significant mitral regurgitation and concomitant functional mitral valve pathology may not be excluded from TAVI. In **Chapter 8** we evaluated the outcome of high operative

risk patients undergoing TAVI for failing bioprosthetic valves. This was the first direct comparison of a small group of patients with failing bioprosthesis in the aortic and mitral valve position treated with transcatheter valve implantation with a similar group of patients treated with redo cardiac surgery. Both groups were comparable in terms of baseline comorbidities, logistic Euroscore predicted surgical risk, functional status and left ventricular ejection fraction. After a median follow-up of 21 months survival was similar in both groups. TAVI is a minimally invasive procedure that may be a viable alternative to redo cardiac surgery for elderly patients with failing bioprostheses deemed inoperable or at excessive surgical risk.

In conclusion, the number of TAVIs has exponentially increased over the last 10 years. Advances in technical aspects, learning curve and improved sizing of aortic annulus with 3-dimensional imaging techniques, particularly MDCT, have improved the results and have made possible the treatment of specific subgroups of patients who were considered initially not suited for TAVI (bicuspid aortic valves, failing bioprostheses). The role of MDCT in the development of TAVI has been crucial. Post-TAVI MDCT data has helped us to understand the underlying mechanisms of specific complications related to TAVI. The future of TAVI is promising with the development of new devices that may accommodate several aortic annulus and root anatomies, that are suited for aortic regurgitation and for failing bioprostheses. In this future, the role of imaging is pivotal and particularly, MDCT is one of the imaging techniques of choice due to its high spatial resolution, permitting the development of holograms that will help the interventionalist to plan the procedure.

Samenvatting en Conclusies

In de introductie van dit proefschrift wordt een overzicht gegeven van de rol die transkatheter aortaklep implantatie (TAVI) in de huidige klinische praktijk vervult en hierbij als extra focus de complicaties paravalvulaire aortaklep insufficiëntie (AI) en post-procedurele geleidingsstoornissen. Tevens wordt er gedetailleerd ingegaan op de rol die multi-detector computed tomography (MDCT) kan hebben in het plannen van de procedure en in het pathofysiologisch verklaren van complicaties. Daarnaast wordt hier ook nog een overzicht beschreven van het "off-label" gebruik van TAVI als behandeling voor patiënten met falende bioprosthese kunstkleppen welke wegens contra-indicatie niet chirurgisch vervangen kunnen worden. Het tot een minimum brengen van de procedurele complicaties en het beter begrijpen van de uitdagingen welke het verbreden van de TAVI-indicatie met zich mee brengt zou ons kunnen helpen de uitkomst van voor TAVI verwezen patiënten te verbeteren.

PART I

In dit deel van het proefschrift is gefocust op hoe het gebruik van MDCT het beleid van TAVI patiënten zou kunnen verbeteren. De informatie van pre- en post-operatieve MDCT scans werd gecombineerd met de klinische en demografische patiëntgegevens en vervolgens gecorreleerd aan complicaties. In **Hoofdstuk 2** bestudeerden we de relatie tussen het ontplooien van het Edwards SAPIEN frame in de aortawortel en de post-procedurele aanwezigheid van paravalvulaire AI. Te midden van diverse klinische en MDCT parameters waren én het verschil tussen de maximale MDCT aorta annulus diameter en de nominale diameter van de prosthese én een ondiepe plaatsing van het frame in de linker kamer outflow tract (LKOT) onafhankelijk gerelateerd aan de aanwezigheid van significante paravalvulaire AI. Deze bevindingen benadrukken de associatie tussen het kiezen van een te kleine prosthese met de post-procedurele aanwezigheid van paravalvulaire AI. Daarnaast kan een te ondiepe plaatsing van de Edwards SAPIEN klep in de LKOT leiden tot suboptimale afdekking van de rand van het frame hetgeen ook tot paravalvulaire kleplekkage kan leiden. In **Hoofdstuk 3** werden de pre- en postimplantatie MDCT's gebruikt voor het ophelderen van de pathofysiologie van belangrijke post-procedurele geleidingsstoornissen. Te midden van diverse anatomische, elektrofysiologische, MDCT en procedurele parameters, waren de implantatie diepte van het frame in de LKOT en overexpansie van het frame met >15% ten opzichte van de oorspronkelijke aorta annulus oppervlakte (gemeten met MDCT) onafhankelijk gerelateerd aan de noodzaak voor een pacemaker of het ontstaan van een nieuw linker bundeltakblok. Pathofysiologisch zouden deze bevinden verklaard kunnen worden doordat een te diepe implantatie van het frame de AV knoop of de linker bundeltak kan beschadigen en ook overexpansie van het frame kan leiden tot compressie krachten

op de LKOT. Met het ophelderen van mechanismen die verantwoordelijk zijn voor het ontstaan van nieuwe geleidingsstoornissen kan de planning van de procedure worden verbeterd en kan wellicht ook het design van toekomstige TAVI prostheses worden gefaciliteerd. De klinische implicaties van de positie van het frame in de aortawortel werden verder onderzocht met post-TAVI MDCT in **Hoofdstuk 4**. Hier werd de relatie tussen het ontplooide frame en de ostia van de coronairen in 142 patiënten systematisch bestudeerd: in 7.7% van de patiënten overlapte het frame een van de coronair ostia volledig en in 35.9% van de patiënten werden de coronair ostia met meer dan 3 mm bedekt door het frame.

Zowel gedeeltelijke als volledige bedekking van de coronair ostia door het frame was niet gerelateerd aan post-procedurele troponine lekkage en op de lange termijn ook niet aan het verrichten van een dotterbehandeling of de mogelijkheid hiertoe. Hiernaast hebben we ook aangetoond dat inklemming van de coronair ostia door het frame relatief zeldzaam is en dat dit niet systematisch is gerelateerd aan post-procedurele ischemie. In **Hoofdstuk 5** wordt ingegaan op het ontstaan van vroege en late pericard effusie na TAVI; een complicatie welke tot dusver nauwelijks bestudeerd is. De aanwezigheid van nieuwe, matige pericard effusie 1 maand na de procedure werd gediagnosticeerd in 2.5% van de patiënten met echocardiografie en MDCT en werd alleen gevonden in diegenen die transapicaal waren behandeld. In geen van de patiënten waren er echter gedocumenteerde tekenen of symptomen van een cardiale tamponade. Er moet worden vermeld dat er wat discrepanties waren in het graderen van pericard effusie tussen de verschillende imaging modaliteiten. De klinische relevantie van deze bevindingen is niet duidelijk.

PART II

In dit deel van het proefschrift wordt de focus gelegd op de uitkomsten van specifieke patient populaties die TAVI ondergaan. Zo wordt in **Hoofdstuk 6** ingegaan op de uitkomsten van TAVI in patiënten met een hoge baseline valvulo-arteriele impedantie (ZVa); dit is een echocardiografische maat voor de globale –met zowel de klep als arteriële- afterload in patiënten met een aortaklep stenose. In patiënten met een baseline ZVa ≥5 mmHg/mL/m^2 was de mortaliteitsfrequentie hoger dan in patiënten met lagere ZVa waarden. Bovendien was de baseline ZVa gedurende de follow-up onafhankelijk geassocieerd met mortaliteit door alle oorzaken. Een hogere ZVa waarde kan geassocieerd zijn met verder gevorderde myocardiale fibrose en dysfunctie. Deze meting zou in toekomstige TAVI risico-scores geïmplementeerd kunnen worden en dit zou de patient-selectie voor deze procedure ten goede kunnen komen. In **Hoofdstuk 7** wordt de aandacht gevestigd op TAVI patiënten die ook significante mitralisklep insufficiëntie

hebben. In het algemeen wordt ernstige mitralisklep insufficiëntie als contra-indicatie voor TAVI beschouwd. Desondanks kunnen patiënten met een ernstige aortaklep stenose en tevens een significante mitralisklep insufficiëntie die inoperabel worden geacht of waarbij er een excessief chirurgisch risico bestaat alsnog met TAVI worden behandeld als middel van laatste redding. Van patiënten met minimaal milde mitralisklep insufficiëntie werd de mitralisklep insufficiëntie kwantitatief geanalyseerd op de echocardiogrammen van aanvang, van voor het ontslag en op de echo van 12 maanden. In de gehele populatie was er post-procedureel acuut een significante vermindering van de mitralisklep insufficiëntie. Een functionele aard van de mitralisklep insufficiëntie en de baseline "effective orifice area" van de insufficiëntie waren onafhankelijk gerelateerd aan de acute verbetering op de echocardiogrammen voor het ontslag. Met deze resultaten wordt benadrukt dat TAVI kandidaten met significante mitralisklep insufficiëntie niet geëxcludeerd hoeven te worden voor het ondergaan van TAVI.

In **Hoofdstuk 8** evalueerden we de uitkomsten van patiënten met een hoog chirurgisch risico die TAVI ondergingen wegens een falende bioprosthese kunstklep. Dit was de eerste directe vergelijking tussen een kleine groep patiënten met falende bioprostheses in aorta- en mitralisklep positie die behandeld was met TAVI met een vergelijkbare groep die behandeld was met redo chirurgie. Beide groepen waren vergelijkbaar in baseline co-morbiditeit, voorspeld chirurgisch risico zoals beoordeeld met de logistische EuroSCORE, functionele status en linker kamer ejectiefractie. Na een mediane follow-up van 21 maanden was de overleving vergelijkbaar in beide groepen. Vanwege het minimaal invasieve karakter kan TAVI een geschikt alternatief zijn voor redo chirurgie in oudere patiënten met falende bioprostheses die inoperabel worden geacht of een excessief chirurgisch risico hebben. Concluderend is in de afgelopen 10 jaar het aantal verrichte TAVI's exponentieel gegroeid. Technische vooruitgang, een leercurve en verbeteringen in het sizen van de aortaklep annulus met 3-dimensionale imaging technieken en dan met name met MDCT, hebben de resultaten van TAVI verbeterd en hebben het tevens mogelijk gemaakt dat specifieke patiënt groepen waarvoor TAVI initieel niet geschikt geacht werd (bicuspide aortakleppen, falende bioprostheses), behandeld kunnen worden. MDCT heeft een cruciale rol gespeeld in de ontwikkeling van TAVI. Post-TAVI MDCT heeft ons geholpen om de onderliggende mechanismen van specifieke complicaties gerelateerd aan TAVI te begrijpen. Met de ontwikkeling van nieuwe devices die kunnen accommoderen in diverse aortaklep annulus en aortawortel anatomieën en devices die geschikt zijn voor de behandeling van AI en falende bioprosthese kunstkleppen is de toekomst van TAVI veelbelovend. Binnen deze toekomst blijft de rol van beeldvorming cruciaal. Met de grote ruimtelijke resolutie van MDCT wordt de ontwikkeling van hologrammen gefaciliteerd en hiermee kan de interventionalist geholpen worden in de planning van de procedure. Hierdoor zal MDCT een van de imaging technieken naar keuze blijven.

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Curriculum Vitae

Spyridon Katsanos was born in Agrinio (Greece) in 26th March 1974. He graduated from Polikladiko high school of Agrinio in 1992 and he studied Medicine in the University of Ioannina where he obtained his medical diploma in 2000. After a twelve month service as a physician in the health center of Kanalaki followed by a fourteen month period of compulsory service in the Greek army as a medical doctor, he undertook his Internal Medicine training in Corfu General Hospital, Greece for two years. The following four years he completed his Cardiology training in KAT hospital Athens, Greece. As a cardiologist he worked for eight months in the heart failure unit of ATTIKON University Hospital of Athens, Greece. He was awarded by a national Hellenic Cardiology grant and moved to Leiden, Netherlands for one year fellowship in imaging research under the mentorship of prof. Dr. Jeroen Bax and Dr. Victoria Delgado. His fellowship was then continued for two more years by the support of second grant from the Hellenic Cardiology Society. His main research field included imaging for transcatheter aortic valve implantation, results of which are presented in this thesis book. He has also a special interest in cardiac computed tomography, periprocedural transesophageal echocardiography, cardiac biomarkers and clinical managing of heart failure patients.

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