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Aortic Valve Disease
Novel Imaging Insights from Diagnosis to Therapy

See Hooi Ewe

Aortic Valve Disease: Novel Imaging Insights from Diagnosis to Therapy

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Aortic Valve Disease: Novel Imaging Insights from Diagnosis to Therapy

Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden, op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker, volgens besluit van het College voor Promoties te verdedigen
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See Hooi Ewe
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To Manish and my parents

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General introduction and outline of the thesis

The prevalence of moderate or severe aortic valve (AV) disease, namely aortic regurgitation (AR) and aortic stenosis (AS), has been estimated as 0.9% in the largest population-based study from the United States.[1] The prevalence of AV disease rose strikingly with age, which is very low (<1%) before the age of 65, and increases to 2.3% for the ages between 65-74, and to 4.8% after the age of 75.[1] Importantly, moderate or severe valvular diseases are not benign but have profound consequences, with cardiac chamber remodeling on echocardiographic examinations (characteristic of volume or pressure overload) and are associated with excess mortality (relative risk of death was 1.36), after adjusted for coronary artery diseases and comorbid conditions despite the availability of surgical valve repair or replacement in the large population-based study.[1] Therefore, the associated excess risk underscores the importance of accurate detection of valvular diseases. In this regard, advanced cardiac imaging plays a critical role in the early diagnosis and recognition, as well as the detection of its deleterious effect on myocardial function, which is the key to improving prognosis, as prompt referral for valve intervention will interrupt and alter the natural history of AV diseases. Therefore beyond the assessment of chamber dimensions or left ventricular (LV) function, conventionally by ejection fraction (EF) assessment, the evaluation of myocardial tissue deformation and strain may help refine risk stratification and decision-making process in patients with AV diseases.

In the Euro Heart Survey, the most common valvular diseases referred to hospital were AV diseases (44%), and AS accounted for the majority (34%).[2] Similarly, valve interventions were performed mostly for AS (47%), and the predominant etiology was degenerative (82%).[2] Therefore, the majority of AS were in the elderly population, affecting 56% in aged ≥70 and 14% were aged ≥80, in whom there are associated increased rates of comorbidities. In the Euro Heart Survey that analyzed the elderly patients with AS, 33% were not referred for surgery, with impaired LV ejection fraction and old age as the main reasons that determine the decision making.[3] Until recently, AVR was the only definitive therapy but many elderly patients are considered high risk surgical candidates. Conversely, if symptomatic AS is left untreated, the prognosis is dismal with an average survival of 2 to 3 years.[4] Thus, there is a need for alternative treatment for AS, and transcatheter aortic valve implantation (TAVI) is a proven effective therapy in AS patients with extreme or high operative risk, with acceptable mortality and complication rates.[5,6] Besides technical advances and procedural experience, accurate patient selection is the key to achieve high success rates and low complications rates with TAVI. Multimodality imaging plays a crucial role in patient selection, guiding the procedure and evaluation of the immediate and long-term results after TAVI.

Transthoracic echocardiography is the primary imaging modality for the diagnosis and assessment of its severity in AV disease, as well as to assess its prognosis by its hemodynamic consequences on the LV. There are many reasons why echocardiography is the preferred modality over the other modalities, due to its ability to provide real-time comprehensive evaluation of the anatomic and physiologic information of all valves, including the aorta and ventricular functions, and its non-invasiveness and wide availability which allows for serial assessment. Current guidelines for intervention in patients with AV disease are based on the presence or absence of symptoms, as well as 2-dimensional (2D) echocardiographic parameters such as the LV size (LV dimensions) and LV function (LVEF).[5,6] However, conventional 2D echocardiography has several limitations and is less reproducible as it is affected by foreshortened apical views and the reliance on geometric assumptions for the calculation of LV volumes and EF.[7]

Regarding the assessment of valvular regurgitation, although it is recommended to quantify the severity of regurgitation,[8,9] this quantitative approach remains challenging in clinical practice due to multiple computations and assumptions inherent in its derivation using the proximal isovelocity surface area (PISA) method.[9] Yet, the widely used conventional semi-quantitative approach of assessment by color flow Doppler is not endorsed, as it is influenced by hemodynamic flow factors.[8,9] Recent advances in echocardiography, in particular, 3-dimensional (3D) echocardiography may have

overcome some of the above-mentioned limitations by permitting direct visualization and measurement of the regurgitant orifice area, without the need for additional computation or geometric assumptions.[10]

In addition, the advent of novel 2D speckle tracking echocardiography (STE) as a new, angle independent technique to evaluate myocardial deformation and strain, have recently been reported to be clinically useful and reproducible.[11] In this respect, the most commonly used measure of LV global systolic function is the global longitudinal strain (GLS), which has been shown to be an incremental predictor of adverse events, beyond LVEF.[12, 13] Moreover, impaired GLS strain may also predict worse outcomes after valve surgery in patients with valvular regurgitation.[14, 15]

Currently, the introduction of TAVI has revolutionized treatment of patients with symptomatic severe AS. In inopertable patients, TAVI has been shown to significantly improve survival over medical therapy.[16] Therefore, TAVI is now a class I recommendation in patients with severe AS and extreme operative risk.[5, 6] Moreover, in patients with high operative risk, TAVI can be considered a viable alternative to surgical aortic valve replacement (SAVR) when TAVI is favored after a multidisciplinary Heart Team assessment,[5,6] as randomized trials have demonstrated that TAVI is non-inferior to SAVR,[17] and is associated with significantly higher one-year survival rate than SAVR.[18] Unlike SAVR where direct inspection is possible, TAVI mandates detailed pre-procedural planning and careful patient and prosthesis selection with the use of multimodality imaging of the AV, aortic root and peripheral arteries, for optimal procedural success. In addition, cardiac imaging plays a key role in the understanding of mechanisms of complications post-TAVI, and provides systematic evaluation and monitoring of the post-procedural results.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY IN AORTIC VALVE DISEASE

Currently, 3D echocardiography are readily available and recent advances have permitted real-time visualization of the entire cardiac structures from any imaging plane. This is a major innovation in the field of cardiovascular ultrasound, offering superior imaging to conventional 2D echocardiography. The clinical usefulness of 3D echocardiography has been demonstrated in: 1) the evaluation of LV volumes and EF[19]; 2) the ability to present unlimited views of heart valves and intracardiac structures using 3D TEE, as it offers superior spatial resolution and 3D anatomic definition, and thus it is the recommended primary imaging modality for guiding transcatheter interventions and for device sizing[20]; 3) the volumetric assessment of regurgitant lesions using 3D color Doppler, with direct quantification by planimetry of the 3D color regurgitation jet (Figure 1), irrespective of a non-circular orifice area or eccentric jet, typically seen in patients with functional mitral regurgitation.[21, 22]

NOVEL IMAGING MODALITIES TO ASSESS LV DEFORMATION

Recently, myocardial strain imaging is proposed as a more sensitive technique to assess the contractile properties of the myocardium, by evaluating the active deformation of the myocardium in all 3 planes of cardiac motion, without being influenced by the tethering or translational cardiac motion. In contrast to previous technique of assessment using Tissue Doppler imaging that is angle-dependent on ultrasound insonation, the novel 2D STE overcomes this by tracking frame-by-frame of the national acoustic markers (the so-called speckles) on gray-scale images and permits measurement of deformation based on excursion between individual speckles throughout the cardiac cycle (Figure 2).[23, 24] In most early disease process, the subendocardial fibers are preferentially affected, and thus the impairment of longitudinal function may occur with preservation of circumferential and radial function.[25] The GLS, as a marker of subendocardial function, has been shown to be incremental and superior to resting LVEF[12, 13] Therefore, the conventional global measures of LV systolic function (such as LVEF, which is used to

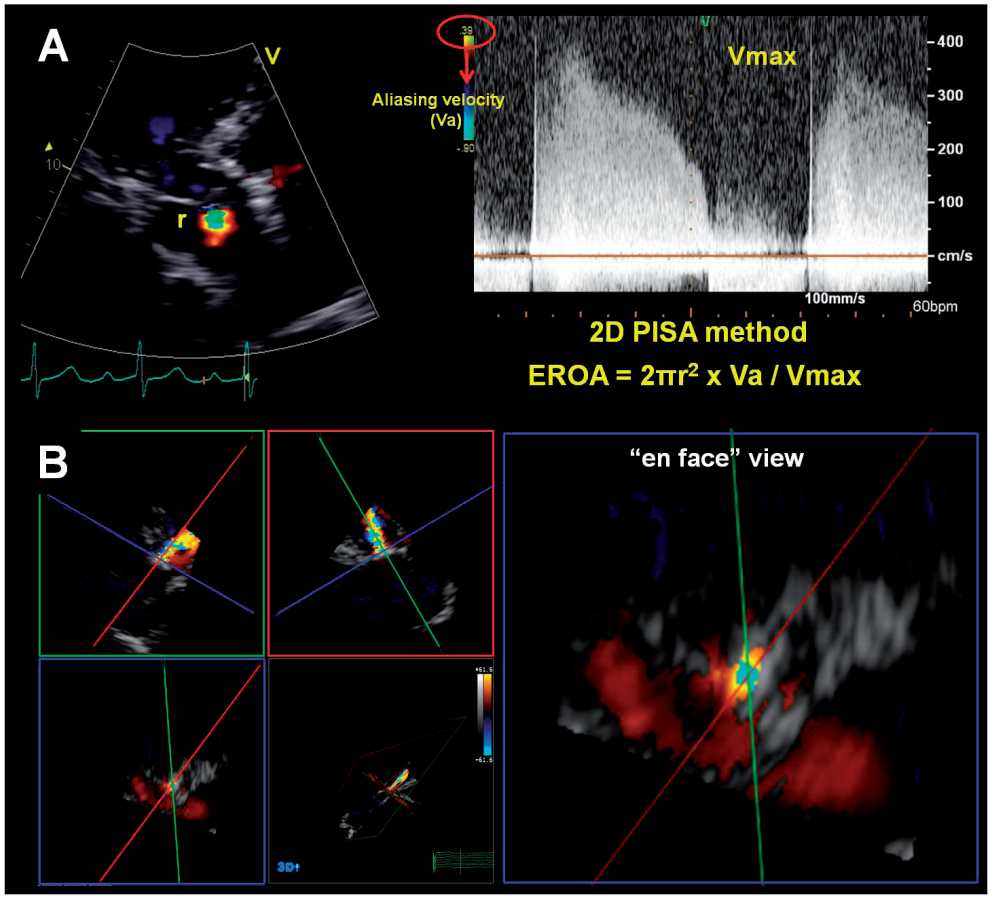

Figure 1. Quantitative assessment of aortic regurgitation severity using the proximal isovelocity surface area (PISA) method using conventional 2-dimensional Doppler echocardiography (panel A). Real-time 3-dmensional (3D) echocardiography permits unlimited plane orientation, allowing for the true cross-sectional area of the regurgitant jet to be planimetered, without multiple computation steps (panel B).

determine intervention in the current guidelines[5,6]) can be preserved until more advanced stage disease, as it lacks sensitivity in ascertaining the transition from compensated state to overt myocardial dysfunction and heart failure.[14,15] Hence, strain imaging using 2D STE may represent a promising tool, to detect subclinical myocardial dysfunction in patients with AV disease.

MULTIMODALITY IMAGING IN TAVI FOR TREATMENT OF AS

The critical steps in ensuring procedural success in TAVI are patient selection, sizing of prosthesis and procedural planning, and noninvasive multimodality imaging plays a key role in providing the important information involving the detailed 3D anatomy of AV, its spatial relationship with the coronary ostia and the ascending aorta, as well as the peripheral arteries. Advances in 3D echocardiography, complement with the superior spatial resolution of multi-

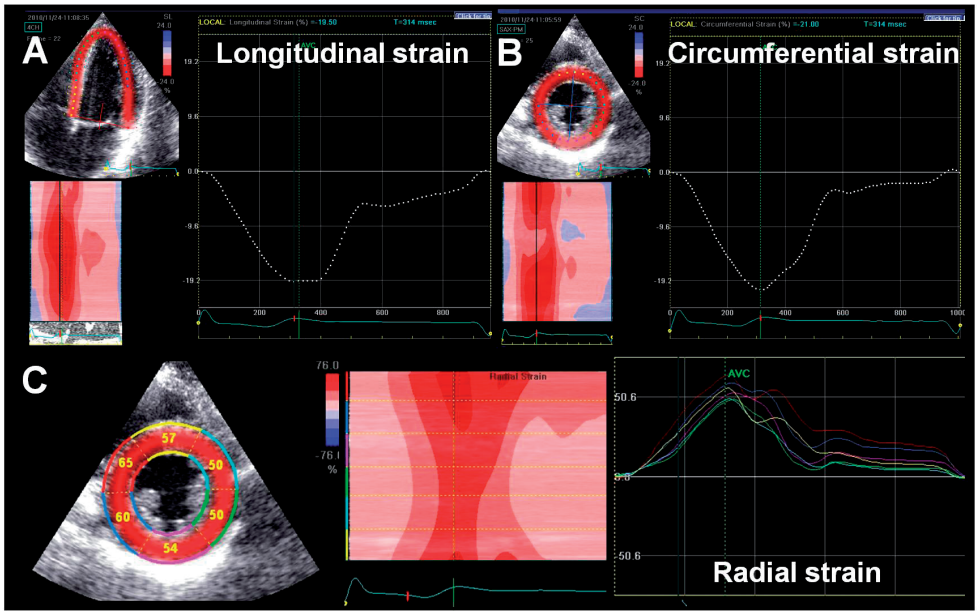

Figure 2. Two-dimensional speckle tracking echocardiography enables comprehensive assessment of active deformation of the myocardium in all 3 planes of cardiac motion, that is angle-independent on ultrasound insonation. Longitudinal strain (panel A) is calculated from apical views of the left ventricle (LV). Circumferential (panel B) and radial strain (panel C) are calculated from mid-ventricular short-axis views of the LV.

detector row computed tomography (MDCT) and magnetic resonance imaging (MRI) have enabled comprehensive pre-procedural evaluation, thus ensuring the best possible outcomes with TAVI.[26,27] However, as with any new technology, pitfalls and limitations are present in the currently used transcatheter valves. Paravalvular regurgitation (PVR) is frequent after TAVI and its presence has been associated with worse clinical outcomes.[28] Precise diagnosis and quantification of PVR is challenging, but advanced cardiac imaging provides insights into the understanding of the mechanism of PVR after TAVI, its assessment of severity, as well as its impact on outcomes over time. Finally, post-TAVI evaluation can also be systematically studied using cardiac imaging from several perspectives and in different patient groups.

OBJECTIVES AND OUTLINE OF THE THESIS

The objectives of this thesis were to investigate the role of advanced cardiac imaging modalities in the management of patients with AV diseases, and its clinical applications in transcatheter AV therapy.

In part I, the incremental value of novel imaging in patients with AR will be discussed. In particular, the additional diagnostic value of 3D echocardiography, over the conventional method of AR quantification using 2D Doppler echocardiography will be explored. Moreover, the value of 2D STE, over the conventional echocardiographic parameters to characterize LV performance in patients with chronic AR will be introduced.

Part II will focus on the clinical applications of multimodality cardiac imaging in TAVI for the treatment of severe AS. First, the evolving role of MDCT in the pre-procedural assessment and planning of patients undergoing transcathether valve therapy will be introduced. Next, the application

of multimodality imaging in patient selection and procedural planning is proposed in the pre-TAVI evaluation algorithm.

After TAVI, the use of cardiac imaging to image, understand and quantify AR post-TAVI, and to guide further maneuvers intra-procedurally will be discussed. In addition, whether the AV calcium and its distribution, have an influence on AR after TAVI will be explored. Finally, the clinical and echocardiographic outcomes after TAVI will be further studied in patients with: 1) significant AR post-TAVI; 2) prosthesis-patient mismatch; 3) baseline impaired LV systolic function; 4) different procedural access, comparing transfemoral (TF) versus transapical (TA) approach.

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PART I

Novel imaging to assess aortic valve regurgitation – incremental role in diagnosis

2

Accuracy of three-dimensional versus two-dimensional echocardiography for quantification of aortic regurgitation and validation by three-dimensional three-directional velocity-encoded magnetic resonance imaging

Ewe SH, Delgado V, van der Geest R, Westenberg JJ, Haeck ML, Witkowski TG, Auger D, Marsan NA, Holman ER, de Roos A, Schalij MJ, Bax JJ, Sieders A, Siebelink HM

Am J Cardiol. 2013 Aug 15;112(4):560-6.

Accuracy of Three-Dimensional Versus Two-Dimensional Echocardiography for Quantification of Aortic Regurgitation and Validation by Three-Dimensional Three-Directional Velocity-Encoded Magnetic Resonance Imaging

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Quantitative assessment of aortic regurgitation (AR) remains challenging. The present study evaluated the accuracy of 2-dimensional (2D) and 3-dimensional (3D) transthoracic echocardiography (TTE) for AR quantification, using 3D 3-directional velocity-encoded magnetic resonance imaging (VE-MRI) as the reference method. Thirty-two AR patients were included. With color Doppler TTE, 2D effective regurgitant orifice area (EROA) was calculated using the proximal isovelocity surface area method. From the 3D TTE multiplanar reformation data, 3D-EROA was calculated by planimetry of the vena contracta. Regurgitant volumes (RVol) were obtained by multiplying the 2D-EROA and 3D-EROA by the velocity-time integral of AR jet and compared with that obtained using VE-MRI. For the entire population, 3D TTE RVol demonstrated a strong correlation and good agreement with VE-MRI RVol ($r = 0.94$ and -13.6 to 15.6 ml/beat, respectively), whereas 2D TTE RVol showed a modest correlation and large limits of agreement with VE-MRI ($r = 0.70$ and -22.2 to 32.8 ml/beat, respectively). Eccentric jets were noted in 16 patients (50%). In these patients, 3D TTE demonstrated an excellent correlation ($r = 0.95$) with VE-MRI, a small bias (0.1 ml/beat) and narrow limits of agreement (-18.7 to 18.8 ml/beat). Finally, the kappa agreement between 3D TTE and VE-MRI for grading of AR severity was good ($k = 0.96$), whereas the kappa agreement between 2D TTE and VE-MRI was suboptimal ($k = 0.53$). In conclusion, AR RVol quantification using 3D TTE is accurate, and its advantage over 2D TTE is particularly evident in patients with eccentric jets. **© 2013 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2013;112:560−566)**

Quantification of aortic regurgitation (AR) remains challenging in clinical practice. Currently, the proximal isovelocity surface area (PISA) method, using 2-dimensional (2D) Doppler echocardiography, is the recommended approach to estimate the regurgitation volume (RVol) and effective regurgitation orifice area (EROA).[1,2] However, several assumptions inherent in its derivation may hamper the accuracy of 2D PISA method to quantify AR, such as noncircular orifices[3] and eccentric jets.[4] Real-time 3-dimensional (3D) echocardiography permits direct visualization of the vena contracta and measurement of the EROA, without the need for additional computation or geometric assumptions.[5−8] In addition, 3D echocardiography is not restricted by any imaging plane, unlike 2D echocardiography, which is limited to quantify flow aligned along the ultrasound beam.[4,8] Therefore, quantification of AR would be more accurate using 3D than 2D echocardiography, and this would probably become more evident in patients with eccentric AR. Recently, 3D 3-directional velocity-encoded magnetic resonance imaging (VE-MRI) has been proposed as a more accurate method to assess transvalvular flow.[7,9,10] The current evaluation assessed the accuracy of 2D and 3D transthoracic echocardiography (TTE) for quantification of AR, using 3D 3-directional VE-MRI as the reference method.

Methods

Thirty-two patients with AR who were clinically referred for TTE and MRI to quantify AR, aortic root, and aortic dimensions were retrospectively evaluated. Patients with acute AR or concomitant valvular disease of more than mild severity, atrial fibrillation, or contraindications for MRI (i.e., implanted devices, claustrophobia) were not included. Clinical data including demographics and symptoms were collected in the departmental electronic patient file (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed. All patients underwent standard 2D and

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See page 565 for disclosure information.

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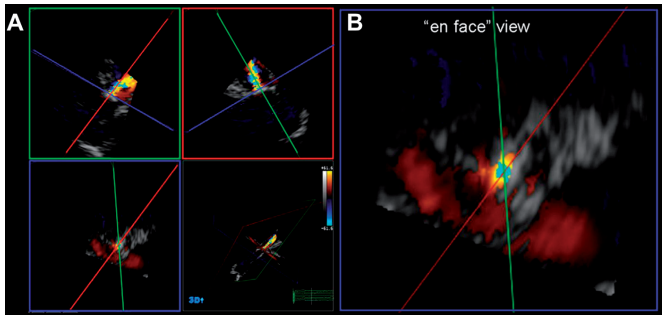

Figure 1. Three-dimensional transthoracic echocardiography for assessment of aortic EROA. First, the 3D color Doppler data set was manually cropped to provide a cross-sectional plane through the vena contracta of the regurgitant jet, perpendicular to the direction of the aortic regurgitant jet *(A)*. Next, from the en face view of the vena contracta, selecting the plane with the narrowest cross-sectional area of the regurgitant jet, the 3D-EROA was measured by manual planimetry of the color Doppler signal *(B)*. The figure provides an example of a patient with central and circular jet.

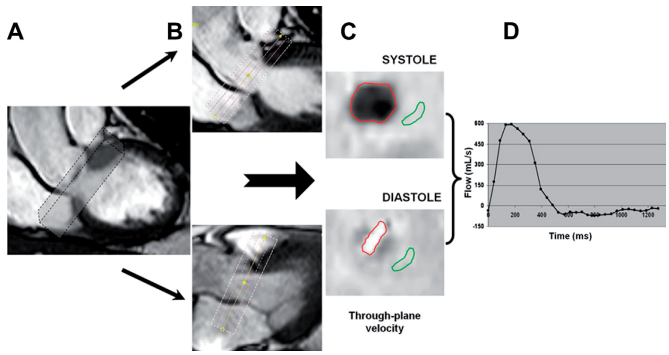

Figure 2. Postprocessing of aortic valve flow from 3D 3-directional VE-MRI data sets. The 3D acquisition volume was positioned at the level of the aortic valve, covering its full excursion during the entire cardiac cycle *(A)*. From the 2 orthogonal views of the aortic valve *(B)*, retrospective valve tracking and reformatting plane (with 5 parallel planes spaced at 5 mm) were reconstructed at the level of the aortic annulus, perpendicular to the aortic flow. The through-plane velocity-encoded images were thus obtained by reformatting in the center of the valvular plane in each cardiac phase *(C)*. During systole, the aortic forward flow was acquired (inner border of the aortic annulus was traced in *red* for flow analysis). During diastole, the regurgitant flow could be identified (*red line*). Region within the left ventricular wall was traced (*in green*) for correction of the myocardial motion, at the caudal-most reformatted plane where myocardial tissue was best visualized. *(D)* Finally, integration of the velocities over the aortic annulus, subtracted by the through-plane velocity of the myocardium, yielded the flow graph. The regurgitant volume was calculated by the Riemann sum of backward flow during diastole in the flow graph.

3D color Doppler TTE to quantify AR RVol and EROA. In addition, cardiac MRI was performed in all patients to assess left ventricular (LV) size and function, aortic valve morphology, AR severity, and aortic root and ascending aorta dimensions.[2] Severity of AR was assessed using 3D 3-directional VE-MRI data to quantify the AR Rvol.

Patients were imaged at rest in the left lateral decubitus position using a commercially available ultrasound system (iE33, Philips Medical Systems, Andover, Massachusetts) equipped with a S5-1 transducer. A complete 2D, color, pulsed, and continuous wave Doppler examination was performed according to the standard guidelines.[1,2,11] For AR quantification, color Doppler images of the aortic valve were acquired with optimized gain and Nyquist scale (50 to 60 cm/s).[1,2] From the zoomed color Doppler view of the AR jet, the vena contracta was identified as the narrowest portion of the regurgitant jet that occurred at or just downstream from the regurgitant orifice.[1,2] For a more quantitative assessment of AR, the PISA method was used. In brief, by shifting the baseline of the aliasing velocity toward the direction of the regurgitant jet (between 20 and 40 cm/s), a well-defined hemisphere of the convergence zone could be identified. From this, the maximal 2D-EROA could be estimated. Subsequently, the RVol was calculated as 2D-EROA multiplied by the velocity-time integral of the AR jet, from the continuous wave Doppler obtained either at the apical 5- or 3-chamber views.[1,2] AR severity was graded based on RVol: grade 1 (mild), <30 ml; grade 2 (mild-to-moderate), 30 to 44 ml; grade 3 (moderate-to-severe), 45 to 59 ml; and grade 4 (severe), ≥ 60 ml.[1,2]

The 3D TTE was performed using the same ultrasound system (the iE33 system) with a fully sampled matrix-array X3 transducer. Apical and parasternal full-volume color Doppler data sets of the AR jets were obtained using electrocardiographic gating over 7 consecutive heart beats to obtain 7 small real-time subvolumes in a larger pyramidal volume. To minimize stitch artifact, the acquisition was performed during 5 to 7 seconds of breath-holding. The color gain and scale were set as previously mentioned. All images were digitally stored and analyzed offline (Q-Lab 3DQ, Philips Medical Systems). To measure 3D-EROA, multiplanar reconstruction of the 3D data sets and manual cropping were performed. First, a cross-sectional plane through the vena contracta of the regurgitant jet, perpendicular to the direction of the AR jet, was obtained. Next, from the en face view of the vena contracta, the 3D-EROA of the narrowest cross-sectional area of the regurgitant jet was measured by manual planimetry from the diastolic frame with the most relevant lesion size (Figure 1). The 3D-RVol was derived by multiplying the 3D-EROA by the velocity-time integral of the AR jet.

MRI was performed using a 1.5-T scanner (Philips Medical Systems, Best, The Netherlands) equipped with a 5-element cardiac synergy coil. First, from a series of short-axis images, encompassing the LV from apex to base and throughout the entire cardiac cycle, quantification of LV volumes and ejection fraction were obtained by using the MASS research software (Division of Image Processing, Department of Radiology, LUMC, Leiden, The Netherlands) with contour segmentation of the epicardial and endocardial borders.[12] For AR quantification, 3D 3-directional VE-MRI was used. A detailed description of the 3D VE-MRI acquisition protocol has been described.[9,10] In brief, a free-breathing 3D phase-contrast acquisition was used with velocity encoding in 3 orthogonal directions. Imaging parameters were as follows: repetition time 7.5 milliseconds, echo time 4.3 milliseconds; field of view 370 mm, 3D volume imaging with 48-mm slab thickness reconstructed into 12 slices of 4 mm, flip angle of 10°, acquisition voxel size $2.9 \times 3.8 \times 4.0$ mm voxel reconstructed into $1.4 \times 1.4 \times 4.0$ mm voxel, 1 acquired signal, and with 30 phases reconstructed during 1 average cardiac cycle from the retrospective gated acquisition (temporal resolution between 25 and 40 milliseconds, depending on the heart rate). Echo-planar imaging was performed with a factor of 5 resulting in scan duration of approximately 5 minutes. The velocity encoding was initially set at 150 cm/s in all 3 directions. However, additional 2D VE-MRI of the aortic valve was used to determine if a higher maximal velocity was required and the optimized velocity was then applied for 3D VE-MRI in all 3 directions.

The 3D VE-MRI acquisitions were postprocessed with the in-house developed MASS research software package.[10] Two orthogonal views of the aortic valve were used for retrospective valve tracking and a reformatting plane (with 5 parallel planes equally spaced at 5 mm apart) was marked at the level of the valve annulus in every cardiac phase, perpendicular to the aortic regurgitant flow (Figure 2). Next, the 3D velocity data were reformatted in the center of the valvular plane to generate 1-directional through-plane velocity-encoded images. If aliasing occurred in any of the velocity directions as a result of high-velocity regurgitant jets, the phase unwrapping option of the software was used to correct the velocity data and to avoid underestimation of regurgitation. Background correction was performed to correct for through-plane motion of the myocardium in basal-to-apical direction and local phase offset.[10] The background region of interest was placed at the most caudal plane (i.e., 10 mm distance from the central plane in the LV anterior wall). Finally, the transvalvular volume flow was obtained by integrating the resulting velocities taken over the annular area. The MRI RVol was obtained by calculating the Riemann sum of backward flow during diastole in the flow graph (Figure 2).[13] The reformatting process required 5 minutes, and subsequent image analysis took another 5 to 10 minutes.

Continuous data are presented as mean ± SD, and categorical variables as absolute numbers (percentages). Chi-square or Fisher's exact tests were used for comparison of categorical variables as appropriate. Linear regression analysis (Pearson correlation) for continuous variables was performed to evaluate the relation between RVol measurements derived from 2D TTE, 3D TTE, and MRI. Bland-Altman plots were used for agreement analysis between 2D TTE, 3D TTE, and MRI derived RVol measurements. In

Table 1
Patient characteristics

Variable	Patients (n = 32)
Age (yrs)	53 ± 18
Male	22 (69%)
Body surface area (m^2)	1.97 ± 0.23
Heart rate (beats/min)	67 ± 13
Systolic blood pressure (mm Hg)	142 ± 20
Diastolic blood pressure (mm Hg)	73 ± 9
New York Heart Association functional class	
I	23 (72%)
II	7 (22%)
III	2 (6%)
Co-morbidities	
Hypertension*	16 (50%)
Hypercholesterolaemia*	9 (28%)
Diabetes mellitus	4 (13%)
Coronary artery disease	4 (13%)
Aortic regurgitation etiology	
Calcific degeneration	14 (44%)
Bicuspid	14 (44%)
Previous infective endocarditis	1 (3%)
Rheumatic	2 (6%)
Idiopathic dilatation of the aorta	1 (3%)
LV end-diastolic volume (ml)	210 ± 77
LV end-systolic volume (ml)	93 ± 46
LV ejection fraction (%)	58 ± 9
Aortic annulus (mm)	26 ± 4
Aortic sinus (mm)	37 ± 6
Sinotubular junction (mm)	31 ± 6
Ascending aorta (mm)	34 ± 7

Data are expressed as mean ± SD or as number (%).

* Hypertension was defined as blood pressure ≥140/90 mm Hg or on antihypertensive medication for hypertension. Hypercholesterolemia was defined as a serum low-density lipoprotein cholesterol >160 mg/dl or on lipid-lowering medication for hypercholesterolemia.

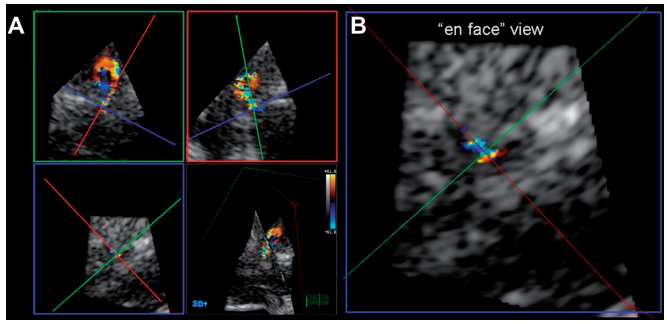

Figure 3. An example of a patient with eccentric aortic regurgitation. Multiplanar reformation of the 3D transthoracic Doppler echocardiography data sets *(A)* revealed an irregularly shaped effective regurgitant orifice area, as shown in the en face view *(B)*.

Table 2
Relationship between aortic regurgitant volume measured by echocardiography and magnetic resonance imaging

Regurgitant Volume	Total Population (n = 32)	Central AR Jet (n = 16)	Eccentric AR Jet (n = 16)
2D TTE vs VE-MRI			
Pearson correlation coefficient (r)	0.70	0.80	0.66
r—95% confidence interval	0.46–0.84	0.51–0.93	0.24–0.87
p value	<0.001	<0.001	0.005
3D TTE vs VE-MRI			
Pearson correlation coefficient (r)	0.94	0.93	0.95
r—95% confidence interval	0.89–0.97	0.82–0.98	0.86–0.98
p value	<0.001	<0.001	<0.001

addition, the kappa statistics were used to assess the agreement among different imaging methods with regard to AR severity grading. In 20 randomly selected patients, interobserver reproducibility for 3D TTE–derived measurements were performed by 2 independent, blinded observers and evaluated by intraclass correlation coefficient (ICC). To evaluate intraobserver reproducibility, the same observer repeated the measurements at 2 time points. Good agreement was defined as ICC >0.8. All statistical analyses were performed using SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois) and MedCalc 10.0 (Mariakerke, Belgium).

Results

Table 1 summarizes the clinical characteristics and parameters of the patients, with bicuspid aortic valve anatomy in 14 patients (44%). AR was equally divided into central (50%) and eccentric (50%) jets. In patients with eccentric jets, a higher proportion of bicuspid compared with tricuspid valve anatomy was observed (75% vs 25%, p = 0.001). Figures 1 and 3 show examples of a central and an eccentric AR jet, respectively.

For the entire population, the mean aortic RVol obtained by 2D, 3D TTE, and VE-MRI were 29.6 ± 14.3, 25.3 ± 14.8, and 24.3 ± 19.6 ml/beat, respectively. There was a significant but modest correlation between the RVol as assessed by 2D TTE and VE-MRI (r = 0.70, p <0.001), and the RVol quantification by 3D TTE showed a strong correlation with VE-MRI (r = 0.94, p <0.001; Table 2). When Bland-Altman plots were performed for entire population, 3D TTE derived RVol showed a small bias (1.0 ml/beat) and narrow limits of agreement (−13.6 to 15.6 ml/beat) versus VE-MRI. In contrast, the bias and limits of agreement between 2D TTE and VE-MRI derived RVol were large (5.3 ml/beat and −22.2 to 32.8 ml/beat, respectively; Figure 4).

In patients with central jets, 2D TTE demonstrated a relatively good correlation with VE-MRI in the assessment of RVol (r = 0.80, p <0.001), but this correlation with VE-MRI could be improved by using 3D TTE (r = 0.93, p <0.001). On the other hand, in patients with eccentric jets, the correlation between RVol as assessed by 2D TTE and VE-MRI was weak (r = 0.66, p = 0.005), whereas the correlation between 3D TTE and VE-MRI derived RVol was strong (r = 0.95, p <0.001; Table 2). On Bland-Altman analysis, 3D TTE derived RVol had the best agreement with VE-MRI regardless of the direction of AR jet (central or eccentric), with the least bias and narrowest limits of agreement (Figure 4). Particularly for eccentric AR, 3D TTE demonstrated a good agreement with VE-MRI, with a small bias (0.1 ml/beat) and narrow limits of agreement (−18.7 to 18.8 ml/beat).

Based on the RVol measurements derived from 2D, 3D TTE, and VE-MRI, the severity of AR was graded accordingly.[1,2] There was a moderate agreement, in terms of AR severity grading, between 2D TTE and VE-MRI (kappa index = 0.53). In 62.5% of patients, including central (n = 13) and eccentric (n = 7) jets, 2D TTE, and VE-MRI provided concordant grading (Figure 5). Of the 12 patients who were differently graded by 2D TTE, the majority of patients had eccentric (n = 9) instead of central jets (n = 3; 75% vs 25%, p = 0.07). In patients with central AR who were misclassified by 2D TTE, the AR severity was marginally overestimated (from mild to moderate).

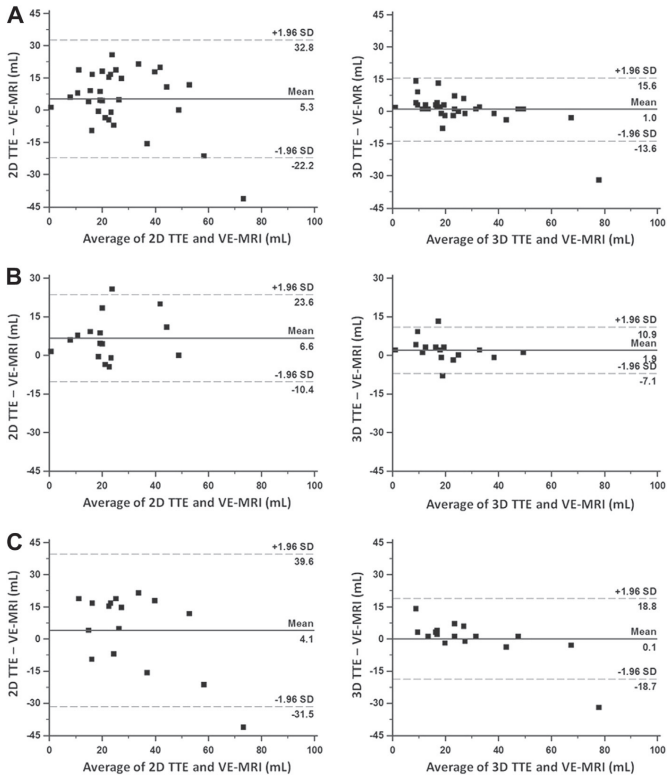

Figure 4. Scatter plots of Bland-Altman analysis for 2D and 3D TTE measurements of aortic regurgitant volume versus the 3D VE-MRI reference values for overall population *(A)*, central *(B)*, and eccentric *(C)* jets.

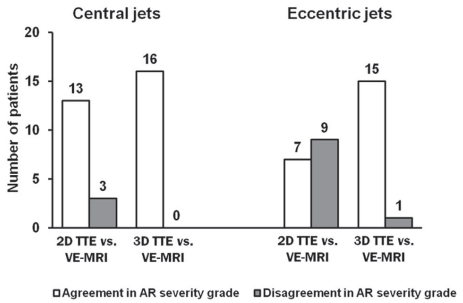

Figure 5. Comparison between 2D and 3D TTE versus the 3D VE-MRI as the reference method.

Among the eccentric AR with incorrect grading, 2D TTE underestimated AR severity in 3 patients compared with VE-MRI, misclassifying grade 3 instead of 4 (n = 2) and grade 1 instead of 2 (n = 1). In the remaining 6 patients, 2D TTE overestimated AR severity compared with VE-MRI (grade 2 instead of 1 in 5 patients, and grade 3 instead of 2 in 1 patient). Importantly, the agreement between 3D TTE and VE-MRI was markedly improved (kappa index = 0.96). All patients were correctly graded with 3D TTE (Figure 5), except 1 patient with eccentric AR (misclassifying as grade 2 instead of 1). Finally, the interobserver and intraobserver reproducibility for 3D echocardiography derived EROA were good as expressed by intraclass correlation (ICC = 0.95 and 95% confidence interval: 0.88 to 0.98 and ICC = 0.97, 95% confidence interval: 0.92 to 0.99, respectively).

Discussion

The present evaluation showed that quantification of AR with 2D TTE is challenging, particularly in eccentric regurgitant jets. In contrast, quantification of AR with direct measurement of the vena contracta area using 3D TTE is feasible and the measurement of AR RVol shows good correlation and agreement with 3D 3-directional VE-MRI, the reference standard. In addition, the measurement of 3D

TTE derived AR RVol showed high inter- and intraobserver reproducibility.

Accurate assessment of valvular regurgitation severity is paramount for prognosis and clinical management of patients with AR.[14,15] This is primarily performed using echocardiography, with the integration of multiple parameters, including the hemodynamic consequences of AR on the LV.[1,2] The assessment of AR severity is usually performed using both quantitative and semiquantitative echocardiographic criteria.[1,2] However, Messika-Zeitoun et al have shown that the commonly used semiquantitative methods in AR assessment, such as pressure half-time, diastolic flow reversal, and LV cardiac output, lack sensitivity.[16] In contrast, the quantitative assessment of AR, using RVol and EROA, not only supersedes the semiquantitative markers of AR severity but also has prognostic clinical implications in patients with AR.[17] Thus, quantitative assessment of AR should always be used, as recommended.[1,2]

The present evaluation shows the superior accuracy of 3D TTE to quantify AR compared with 2D TTE, particularly in eccentric regurgitant jets. 3D TTE-derived AR RVol had the best agreement with that obtained by 3D 3-directional VE-MRI. It is not surprising that 3D TTE provides a more accurate quantification for AR than 2D PISA method because direct planimetry of the AR vena contracta can be performed without any geometric or flow assumptions or multiple computation steps.[1,5–8] By using multiplanar reconstruction of the 3D full-volume data set, 3D TTE has the advantage of unlimited plane orientation, allowing the exact shape and size of the true cross-sectional view of the regurgitant orifice to be measured accurately. In addition, the use of 3D 3-directional VE-MRI sequences as the method of reference, with retrospective valve tracking,[7,9,10] further strengthens the results of the present evaluation because the 3D VE-MRI sequence permits direct measurement of the through-plane transaortic blood flow, taking into consideration the valve and heart motion throughout the cardiac cycle. Moreover, MRI is the reference standard to evaluate LV size and function (a measure of the hemodynamic consequence of AR) and dimensions of the thoracic aorta,[18] all of which are important parameters to consider in clinical decision making for managing patients with AR.[14,15]

Most important, the present evaluation demonstrated a high accuracy of using 3D TTE to quantify AR especially in patients with eccentric jets, whereas 2D TTE was less precise in AR quantification in these patients. Indeed, this translated into less accurate grading of eccentric AR with 2D TTE based on the PISA-derived method, causing significant misclassification in 56.3% of patients (9 of 16). With 3D TTE, misclassification only occurred in 3.1% (1 of 16 patients). These results are in line with the series reported by Pouleur et al., including 21 patients with central jets and 29 patients with eccentric jets.[4] The PISA derived RVol obtained by 2D echocardiography had only fair correlation ($r = 0.69$) with that measured by MRI in patients with eccentric jets, whereas the correlation between 2D echocardiography and MRI in central AR jets was good ($r = 0.92$). In addition, that study also demonstrated that in eccentric jets, the differences between 2D TTE–derived PISA and MRI-derived RVol could be nullified by imaging from the left parasternal window, yielding a better view of the AR jet and flow convergence compared with the conventional apical window, thus underscoring the limitation of 2D TTE in aligning the eccentric jets with ultrasound beam.[4] Of interest, the present evaluation demonstrated that 3D TTE permitted accurate quantification of AR, even in the presence of an eccentric jet. Moreover, nonplanar flow convergence angle, commonly seen in AR patients with concomitant aneurismal dilatation of the ascending aorta, could represent another source of error in the calculation of AR quantification using the PISA derived method.[19] However, this would not be a consideration if the 3D TTE approach was used.

The retrospective design of the present evaluation precluded investigation of the clinical and prognostic implications of these findings, which should be further evaluated in prospective studies.

Disclosures

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3

Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle-tracking echocardiography analysis

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Detection of subtle left ventricular systolic dysfunction in patients with significant aortic regurgitation and preserved left ventricular ejection fraction: speckle tracking echocardiographic analysis

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Aims The aim of this study was to characterize left ventricular (LV) mechanics in symptomatic and asymptomatic patients with moderate-to-severe or severe aortic regurgitation (AR) and preserved ejection fraction (left ventricular ejection fraction) using two-dimensional speckle tracking echocardiography (2D-STE). The association between baseline LV strain and development of indications for surgery in asymptomatic patients was also evaluated.

Methods and results A total of 129 patients with moderate-to-severe or severe AR and LVEF >50% (age 55 ± 17 years, 64% male, 53% asymptomatic at baseline) were included. Standard echocardiography and 2D-STE were performed at baseline. Compared with asymptomatic patients, symptomatic patients had significantly impaired LV longitudinal (−14.9 ± 3.0 vs. −16.8 ± 2.5%, $P < 0.001$), circumferential (−17.5 ± 2.9 vs. −19.3 ± 2.8%, $P = 0.001$), and radial (35.7 ± 12.2 vs. 43.1 ± 14.7%, $P = 0.004$) strains. Among 49 asymptomatic patients who were followed up, 26 developed indications for surgery (symptoms onset or LVEF ≤50%). These patients had comparable LV volumes, LVEF, and colour Doppler assessments of AR jet at baseline, but more impaired LV longitudinal ($P = 0.009$) and circumferential ($P = 0.017$) strains compared with patients who remained asymptomatic. Impaired baseline LV longitudinal (per 1% decrease, HR = 1.21, $P = 0.04$) or circumferential (per 1% decrease, HR = 1.22, $P = 0.04$) strain was independently associated with the need for surgery.

Conclusion Multidirectional LV strain was more impaired in symptomatic than in asymptomatic patients with moderate-to-severe or severe AR, despite preserved LVEF. In asymptomatic AR patients, longitudinal and circumferential strains identified patients who would require surgery during follow-up.

Keywords Aortic regurgitation • Echocardiography • Speckle tracking • Surgery • Ejection fraction

Introduction

Currently, the class I indications for aortic valve (AV) surgery in severe aortic regurgitation (AR) are when patients are symptomatic and/or when there is impairment of left ventricular ejection fraction (LVEF ≤50%).[1,2] However, as the LV enlarges with time, and in the presence of inadequate preload reserve and/or excessive increase in afterload, impairment of LV function may occur even before the onset of symptoms.[3] Previous studies have also reported that some indices of LV function (such as myocardial strain and mitral

annular plane systolic excursion) may be abnormal in asymptomatic patients with chronic severe AR, despite preserved LVEF.[4,5] When symptoms of heart failure develop in these patients, irreversible damage to myocardial structure (fibrosis)[6] and function may have already occurred,[7] which may preclude the recovery of LV function following AV surgery.[8–10] Thus, accurate detection of subclinical LV dysfunction before the onset of symptoms and a drop in LVEF may be clinically helpful to identify asymptomatic severe AR patients who are at risk, necessitating early referral for surgery.

Strain imaging is a more sensitive technique (when compared with LVEF) to evaluate the contractile properties of the myocardium in patients with chronic AR.[5,11,12] Recently, myocardial deformation can be assessed using two-dimensional speckle tracking echocardiography (2D-STE), which allows angle-independent assessment of LV deformation by tracking the frame-to-frame natural acoustic markers (the so-called speckles) within the myocardium wall.[13–15] Myocardial strain values may indirectly reflect structural changes in the myocardium including fibrosis.[14,15] We hypothesized that impairment in LV strain can be demonstrated in patients with moderate-to-severe and severe chronic AR, despite being asymptomatic and having preserved LVEF, and that 2D-STE would be a helpful tool to identify those asymptomatic high-risk individuals who progress to require AV surgery. Therefore, the aims of this study were as follows:

(1) To evaluate the presence of subtle LV systolic dysfunction, using 2D-STE, in symptomatic and asymptomatic patients with moderate-to-severe or severe chronic AR and preserved LVEF, and
(2) To evaluate the potential role of baseline LV strain, using 2D-STE, in identifying asymptomatic AR patients who later develop indications for AV surgery.

Methods

Patient population and data collection

The patient population comprised 129 patients with moderate-to-severe or severe AR who were identified in the echocardiographic database of the Cardiology Department at the Leiden University Medical Center (Leiden, the Netherlands). Patients with acute AR, concomitant valvular disease of more than mild in severity, known ischaemic heart disease, previous cardiac or valve surgery, reduced LVEF ($\leq$50%), and inadequate echocardiographic data for 2D-STE analysis were excluded.

All clinical data were retrospectively retrieved from the departmental electronic patient dossier information system (EPD-vision®; Leiden, the Netherlands) and analysed. All patients were followed up by the treating physicians according to routine clinical practice. A detailed clinical history was retrospectively retrieved, focusing on patients' symptoms that were deemed to be related to AR by the attending physicians. Subsequently, patients were divided into two groups based on the presence or absence of symptoms at the time of first echocardiographic examination. LV myocardial functions (radial, circumferential, and longitudinal strains) were evaluated using 2D-STE and compared between symptomatic and asymptomatic patients. In addition, in the group of patients who were asymptomatic at the initial echocardiographic examination, the clinical information was retrospectively analysed to identify those who later developed symptoms or deterioration in LV function (LVEF $\leq$50%), meeting the indications for AV surgery (according to the current guidelines).[1,2,16] The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patients' written informed consent.

Echocardiography

Transthoracic echocardiographic images were acquired at rest with the patient in the left lateral decubitus position using a commercially available ultrasound system (Vivid-7 and E9, General Electric Vingmed, Horten, Norway) and were digitally stored for offline analysis (EchoPAC version 110.0.0, GE-Vingmed). Standard 2D, colour, pulsed, and continuous-wave Doppler echocardiographic acquisitions were performed.[16–18] LV dimensions were obtained from the standard M-mode images at a parasternal long-axis view,[18] and LV mass index was calculated according to Devereux *et al.* and corrected for body surface area (BSA).[18,19] In addition, the relative wall thickness was calculated as a ratio of (2 $\times$ PWTd)/LVIDd, where PWTd is the posterior wall thickness and LVIDd is the LV internal diameter at end-diastole. Next, LV end-diastolic and end-systolic volumes were measured from the apical views (two- and four-chamber) using biplane Simpson's method and corrected for BSA.[18] LVEF was subsequently calculated and expressed as a percentage.

Detailed examination of the AV, aortic root, and proximal ascending aorta were performed according to the standard guidelines.[16,18] To assess AR severity, comprehensive, colour, continuous, and pulsed-wave Doppler recordings were performed according to the recommendations that included the measurement of vena contracta width, regurgitant jet width, pressure half-time, and diastolic flow reversal in the descending aorta.[16,17] The final grading of AR severity required integration of data from imaging of the aortic root, AV, and LV.[16,17]

Two-dimensional speckle tracking echocardiography

Myocardial deformation can be assessed using 2D-STE, performed on greyscale images of the LV obtained in the apical two-, three-, and four-chamber views and parasternal mid-ventricular short-axis view.[13–15] An LV longitudinal strain was evaluated in the three apical views, whereas LV circumferential and radial strains were evaluated in the mid-ventricular short-axis view. From the 2D images, the endocardial border was manually traced at end-systole, and the region-of-interest width was adjusted to include the entire myocardial wall thickness. After verification of myocardial tracking, the software package (EchoPAC version 110.0.0, GE-Vingmed) automatically tracked the myocardium. Manual adjustment was performed if necessary. In each echocardiographic view, the myocardium was automatically divided into six segments. Thus, global peak systolic longitudinal strain was calculated by averaging the peak systolic values of all the 18 segments, derived from the three apical views (six segments in each apical view). Global peak systolic circumferential and radial strains were calculated by averaging the peak systolic values of all the six segments from the mid-ventricular short-axis view. Accordingly, the global systolic LV performance was evaluated in all the three myocardial directions using advanced 2D-STE.

Follow-up and end points

Patients who were asymptomatic were divided into two groups: those who met and those who did not meet indications for AV surgery at follow-up.[1,2,16] From the clinical and echocardiographic variables recorded at the time of first echocardiographic examination, independent determinants of AV surgery were identified.

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages. Differences in baseline variables between the two groups were analysed using unpaired Student's *t*-tests (for continuous variables) and χ^2 or Fisher's exact test (for categorical variables). In the group of patients who were initially asymptomatic at the first echocardiographic examination and were

followed up conservatively, uni- and multivariate Cox regression analyses (with an enter method) were performed to identify baseline clinical and echocardiographic determinants of AV surgery. The independent association between LV systolic strains and need of AV surgery, was assessed in a multivariate Cox regression analysis including known predictors of need for AV surgery (such as age, gender, LV end-systolic volume index, and AR vena contracta width)[1] into the model. Receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off value of baseline LV strain to predict AV surgery at follow-up. All statistical analyses were performed using SPSS for Windows, version 16 (SPSS, Inc., Chicago, IL, USA). A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

Patient population

A total of 129 patients (age 55 $\pm$ 17 years, 64% male) with moderate-to-severe or severe chronic AR were evaluated. Of these, 61 (47%) patients reported to have symptoms at the time of the first echocardiographic examination. *Table 1* summarizes the clinical characteristics of patients with and without symptoms recorded at baseline. There were no significant differences in age, gender, and cardiovascular risk factors between the two groups. In terms of the mechanism underlying AR, asymptomatic patients were more likely to have bicuspid AVs but less likely to have inflammatory/infective causes (*Table 1*).

Echocardiography in patients with and without symptoms

Table 2 summarizes the comparison of echocardiographic parameters in patients with and without symptoms at baseline. Patients with symptoms had a significantly larger LV end-diastolic volume index and a trend towards a larger LV end-systolic volume index when compared with those without symptoms. Accordingly, the LVEF was lower in patients with symptoms, although all patients had by definition a preserved LVEF ($>$50%). In terms of colour Doppler assessment of the AR, patients with symptoms had a significantly larger vena contracta width, a higher jet to LV outflow tract width ratio, and a shorter pressure half-time when compared with those without symptoms (*Table 2*).

Regarding the assessment of LV performance using 2D-STE, patients with symptoms demonstrated a significantly larger impairment in myocardial function in all three directions when compared with those without symptoms (*Table 2*). Patients with symptoms had a significant worse longitudinal strain compared with those without symptoms (-14.9 ± 3.0 vs. -16.8 ± 2.5%, $P < 0.001$). Similarly, circumferential (-17.5 ± 2.9 vs. -19.3 ± 2.8%, $P = 0.001$) and radial (35.7 ± 12.2 vs. 43.1 ± 14.7%, $P = 0.004$) strains were more impaired in patients with symptoms than in those without symptoms.

Asymptomatic patients

Of the 68 patients who were initially asymptomatic, 49 patients had clinical data at follow-up permitting retrospective analysis. Over a mean follow-up period of 4.2 ± 3.2 years (interquartile range 1.2–6.6 years), 26 (53%) patients progressed to meet indications for AV surgery (onset of symptoms in 21 patients and LVEF $\leq$50% in 5 patients). The remaining 23 patients were symptom-free with preservation of LVEF. *Table 3* summarizes the baseline clinical and echocardiographic data of the 49 asymptomatic AR patients. Of note, no significant differences in clinical characteristics were

Table 1 Baseline clinical characteristics of the study population

	Symptomatic ($n = 61$)	Asymptomatic ($n = 68$)	*P*-value*
Age (years)	55 ± 16	54 ± 17	0.74
Male, *n* (%)	42 (69)	40 (59)	0.27
BSA (m^2)	1.93 ± 0.21	1.89 ± 0.22	0.26
Heart rate (bpm)	74 ± 13	70 ± 12	0.11
Systolic blood pressure (mmHg)	131 ± 22	134 ± 17	0.50
Diastolic blood pressure (mmHg)	70 ± 14	70 ± 11	0.89
MDRD glomerular filtration rate (mL/min/1.73 m^2)	81 ± 24	85 ± 20	0.35
Cardiovascular risk factors			
Hypertension, *n* (%)	41 (67)	40 (59)	0.37
Hypercholesterolaemia, *n* (%)	21 (34)	19 (28)	0.45
Diabetes, *n* (%)	7 (11)	4 (6)	0.35
Current smoking, *n* (%)	23 (38)	18 (26)	0.47
AR aetiology			
Degenerative, *n* (%)	23 (38)	32 (47)	0.38
Bicuspid, *n* (%)	13 (21)	27 (40)	0.035
Rheumatic, *n* (%)	3 (5)	2 (3)	0.67
Inflammatory/infective, *n* (%)	12 (20)	2 (3)	0.003
Annuloaortic ectasia, *n* (%)	10 (16)	6 (9)	0.29

AR, aortic regurgitation; MDRD, Modification of Diet in Renal Disease.[20]
**P*-values for comparison between symptomatic and asymptomatic patients.

Table 2 Baseline echocardiographic parameters of the study population

	Symptomatic ($n = 61$)	Asymptomatic ($n = 68$)	*P*-value*
Conventional echocardiography			
LV end-diastolic diameter (mm)	57 ± 8	55 ± 8	0.11
LV end-systolic diameter (mm)	36 ± 9	34 ± 7	0.25
Relative wall thickness	0.39 ± 0.09	0.40 ± 0.06	0.30
LV end-diastolic volume index (mL/m^2)	95 ± 33	83 ± 27	0.034
LV end-systolic volume index (mL/m^2)	40 ± 16	34 ± 17	0.064
LVEF (%)	59 ± 6	61 ± 5	0.012
LV mass index (g/m^2)	134 ± 36	130 ± 37	0.50
LV outflow tract (mm)	24.1 ± 3.2	24.1 ± 3.4	0.97
Aortic sinus (mm)	38.1 ± 6.1	37.5 ± 6.3	0.55
Sinotubular junction (mm)	32.9 ± 6.4	31.6 ± 6.7	0.27
Ascending aorta (mm)	37.2 ± 9.5	34.6 ± 7.1	0.083
Vena contracta width (mm)	6.2 ± 1.1	5.5 ± 1.0	<0.001
Jet to LV outflow tract width ratio (%)	58 ± 11	50 ± 10	<0.001
Pressure half-time (ms)	278 ± 95	367 ± 90	<0.001
Two-dimensional speckle tracking echocardiography			
LV longitudinal strain (%)	−14.9 ± 3.0	−16.8 ± 2.5	<0.001
LV circumferential strain (%)	−17.5 ± 2.9	−19.3 ± 2.8	0.001
LV radial strain (%)	35.7 ± 12.2	43.1 ± 14.7	0.004

*P-values for comparison between symptomatic and asymptomatic patients.

observed, except that those who required surgery were older. In particular, baseline LV volume indexes, LVEF, and colour Doppler assessment of the AR were not significantly different between the two groups (*Table 3*). However, 2D-STE demonstrated that baseline LV myocardial strain was significantly more impaired in the longitudinal (−15.7 ± 2.0 vs. −17.6 ± 2.7%, $P = 0.009$) and circumferential (−18.3 ± 2.4 vs. −20.2 ± 2.9%, $P = 0.017$) directions in patients who later required surgery than those who remained symptom-free without surgery (*Table 3*).

Next, Cox regression analyses were performed to identify baseline clinical and echocardiographic determinants of AV surgery. On univariate analysis, age and LV longitudinal and circumferential strains were significantly related to AV surgery (*Table 4*). *Table 4* presents that besides a larger AR vena contracta width, both impaired LV longitudinal and circumferential strains were independently associated with AV surgery at follow-up, after correcting for age, gender, and LV volumes. Importantly, either LV longitudinal or circumferential strain provided a modest and significant incremental value over clinical and echocardiographic variables in predicting AV surgery (*Figure 1*). By ROC curve analysis, LV longitudinal strain ≥ −17.4% provided the highest sensitivity (77%) and specificity (57%) to predict the future need of AV surgery [area under the curve (AUC) = 0.70, $P = 0.008$]. *Table 5* summarizes the predictive ability of LV longitudinal strain to identify patients who will require AV surgery, using several proposed cut-off values. Importantly, LV longitudinal strain ≥ −19.3% provided the highest sensitivity (100%) to predict AV surgery, with a negative predictive value of 100%. Therefore, patients with a better longitudinal strain of −19.3% would be free from symptoms and surgery.

Discussion

The present analysis demonstrated that, despite preserved LVEF, multidirectional LV strain was more impaired in patients with moderate-to-severe or severe AR with symptoms than those without symptoms. Furthermore, in asymptomatic patients with moderate-to-severe and severe AR, LV strain (in particular, longitudinal strain), as assessed using 2D-STE, appeared to be a valuable tool to identify patients who are at risk of requiring AV surgery.

Multidirectional myocardial strain in chronic AR

Chronic AR often progresses slowly over the years, and the LV adapts by replication of sarcomeres in series in the presence of chronic volume overload. This allows for elongation of myocytes, thereby increasing LV volume to generate a larger stroke volume to maintain forward output.[21–23] The gradual LV enlargement is followed by LV wall thickening, resulting in the development of eccentric hypertrophy. This is an adaptive process in the early course of the disease, normalizing wall stress and permitting normal filling pressures despite a substantial increase in LV volume overload.[22] In addition, LVEF is normally preserved during the compensated phase of chronic AR, and many patients may remain asymptomatic for years. With time, however, the combination of progressive LV enlargement and the increase in LV pressure will reach a point when it is no longer offset by an adequate increase in LV wall thickness and will result in an increase in systolic LV wall stress.[21] This afterload mismatch, together with a limited preload reserve in dilated ventricles, marks

Table 3 Baseline characteristics of asymptomatic patients with clinical and echocardiographic data at follow-up

	Need AV surgery (n = 26)	No need AV surgery (n = 23)	P-value*
Age (years)	55 ± 16	42 ± 15	0.006
Male, *n* (%)	16 (62)	15 (65)	1.00
BSA (m^2)	1.91 ± 0.17	1.89 ± 0.25	0.75
Heart rate (bpm)	69 ± 15	70 ± 11	0.82
Systolic blood pressure (mmHg)	129 ± 14	133 ± 18	0.47
Diastolic blood pressure (mmHg)	68 ± 12	70 ± 9	0.60
MDRD glomerular filtration rate (mL/min/1.73 m^2)	84 ± 19	86 ± 23	0.83
Cardiovascular risk factors			
Hypertension, *n* (%)	15 (58)	11 (48)	0.57
Hypercholesterolaemia, *n* (%)	8 (31)	4 (17)	0.33
Diabetes, *n* (%)	3 (12)	1 (4)	0.61
Current smoking, *n* (%)	8 (31)	4 (17)	0.33
Conventional echocardiography			
LV end-diastolic diameter (mm)	55 ± 7	55 ± 6	0.90
LV end-systolic diameter (mm)	35 ± 7	33 ± 6	0.28
LV end-diastolic volume index (mL/m^2)	81 ± 30	83 ± 18	0.84
LV end-systolic volume index (mL/m^2)	32 ± 15	35 ± 22	0.54
LV ejection fraction (%)	61 ± 5	62 ± 5	0.50
LV mass index (g/m^2)	131 ± 33	130 ± 32	0.93
LV outflow tract (mm)	23.6 ± 2.7	24.8 ± 3.5	0.20
Ascending aorta (mm)	35.4 ± 7.7	33.4 ± 5.6	0.30
Vena contracta width (mm)	5.5 ± 1.2	5.3 ± 1.0	0.37
Jet to LV outflow tract width ratio (%)	52 ± 10	48 ± 10	0.24
Pressure half-time (ms)	367 ± 118	374 ± 69	0.83
Two-dimensional speckle tracking echocardiography			
LV longitudinal strain (%)	−15.7 ± 2.0	−17.6 ± 2.7	0.009
LV circumferential strain (%)	−18.3 ± 2.4	−20.2 ± 2.9	0.017
LV radial strain (%)	38.6 ± 13.8	43.5 ± 13.2	0.22

Abbreviations as listed in *Table 1*.
*P-values for comparison between patients who developed indications for surgery and those who remained asymptomatic during follow-up.

the onset of impairment in LV performance in patients with chronic AR.[23,24] When the LV adaptive mechanisms fail or are inadequate, symptoms generally occur and LVEF becomes reduced. This, however, is an insidious process. Although LVEF is a widely accepted and utilized method for the assessment of LV systolic function, it is a reflection of the global ejection performance of the LV, which is derived from volume-based parameters. Given that it is calculated using geometric assumptions and it is affected by loading conditions, LVEF alone may not reflect the true LV performance.[18]

New parameters such as strain imaging are more sensitive techniques than LVEF to assess LV function and to detect subtle changes in myocardial performance, particularly early in the disease process. In fact, several studies reported that impairment of myocardial deformation (thickening or shortening) was observed in asymptomatic patients with chronic moderate and severe AR with preserved LVEF.[11,12] In contrast to studies assessing myocardial deformation with tissue Doppler imaging-derived strain, novel 2D-STE was employed in the present study. 2D-STE overcomes the angle insonation dependency of tissue Doppler imaging and permits the assessment of myocardial strain in all directions (longitudinal, circumferential, and radial).[13,14] Importantly, the present study showed that LV myocardial strain was more impaired in all the three directions in symptomatic patients with moderate-to-severe and severe AR when compared with asymptomatic patients, although all patients had a preserved LVEF by virtue of the inclusion criteria.

Symptomatic vs. asymptomatic patients and baseline predictors of AV surgery

In the present study, it is not surprising that the group of patients with symptoms exhibited features of more severe AR when compared with the group of asymptomatic patients. Symptomatic patients showed larger vena contracta width and LV dimensions, and lower LVEF. Despite significant differences in LVEF, both groups of patients had preserved LVEF (>50%). However, when LV function was evaluated using 2D-STE, symptomatic patients had significantly more reduced LV performance when compared with asymptomatic patients. In a recent longitudinal study of 64 patients who had moderate-to-severe AR with a wide range of LVEF,[25] Olsen *et al.*[25] showed that global LV longitudinal systolic strain was lower in patients with symptoms of heart failure (n = 26) when compared

Table 4 **Uni- and multivariate determinants of AV surgery in asymptomatic patients with clinical and echocardiographic data at follow-up ($n = 49$)**

Variable	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Model included longitudinal strain				
Age (years)	1.03 (1.00–1.05)	0.023	1.02 (1.00–1.05)	0.059
Male gender	1.16 (0.51–2.64)	0.725		
LV end-systolic volume index (mL/m^2)	0.97 (0.98–1.02)	0.706		
Vena contracta width (mm)	1.31 (0.89–1.94)	0.173	1.61 (1.02–2.52)	0.041
Longitudinal strain (per 1% worsening)	1.21 (1.02–1.45)	0.030	1.20 (1.01–1.44)	0.044
Model included circumferential strain				
Age (years)	1.03 (1.00–1.05)	0.023	1.02 (1.00–1.05)	0.094
Male gender	1.16 (0.51–2.64)	0.725		
LV end-systolic volume index (mL/m^2)	0.97 (0.98–1.02)	0.706		
Vena contracta width (mm)	1.31 (0.89–1.94)	0.173	1.50 (0.95–2.37)	0.079
Circumferential strain (per 1% worsening)	1.18 (1.02–1.36)	0.025	1.22 (1.01–1.46)	0.039

CI, confidence interval; LV, left ventricular; HR, hazard ratio.

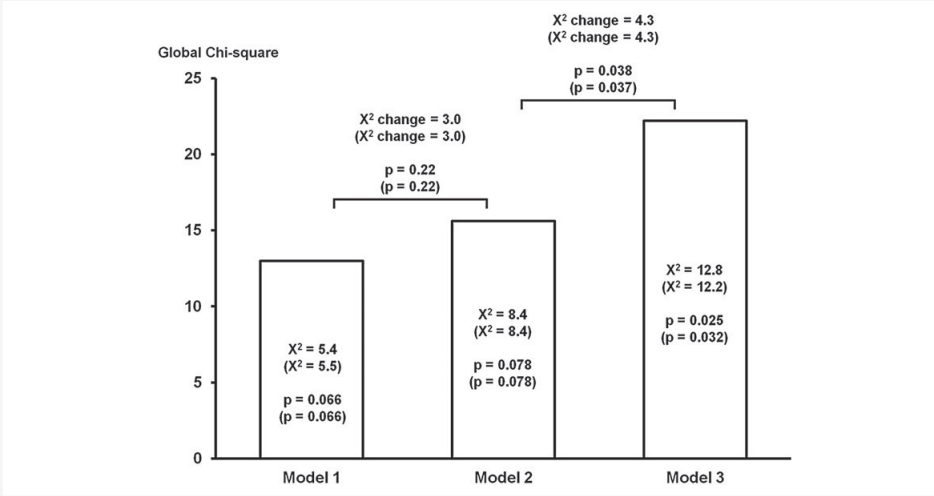

Figure 1 Incremental value of LV peak systolic longitudinal (or circumferential) strain over clinical and echocardiographic variables in predicting AV surgery in asymptomatic patients with clinical and echocardiographic data at follow-up ($n = 49$). Model 1 included clinical variables (age and male gender). Model 2 included clinical and echocardiographic variables (LV end-systolic volume index and vena contracta width of the AR jet). Model 3 included clinical and echocardiographic variables and advanced speckle tracking strain imaging-derived LV peak systolic longitudinal strain. Corresponding values for peak systolic circumferential strain are given in parentheses.

with patients without symptoms ($n = 38$). Our findings extend this observation to a larger cohort of chronic moderate and severe AR patients with preserved LVEF.

More importantly, the present study showed that among asymptomatic patients with moderate-to-severe or severe AR and preserved LVEF, the group of patients who would later require AV surgery during follow-up had more impaired LV longitudinal and circumferential strains when compared with patients who remained asymptomatic. Very often in clinical practice, the distinction between the onset of mild symptoms and the total absence of symptoms is challenging,

Table 5 Predictive ability of baseline LV longitudinal strain in identifying asymptomatic patients who will require AV surgery

Longitudinal strain cut-off value (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
−19.3	100	26	61	100
−17.4	77	57	67	68
−15.1	35	87	75	54

and if the decision to proceed with corrective surgery is based exclusively on LVEF or symptoms onset alone, it is possible that significant LV dysfunction has already developed, thereby precluding full benefit of AV surgery. In a series of 52 patients with chronic severe AR undergoing surgery, Onishi *et al.*[26] demonstrated that preoperative LV radial strain rate had the largest AUC among other parameters (including LVEF or LV dimensions) in predicting postoperative LV dysfunction at 12 months.[26] A recent study by Kusunose *et al.*[27] also showed that resting global LV strain, using velocity vector imaging, was independently associated with the need for early valve surgery in asymptomatic patients with moderately severe-to-severe AR. In line with this, the present study demonstrated that the presence of subtle myocardial changes occurring early in the disease process could be detected by 2D-STE, when other conventional parameters remain indistinguishable during the follow-up of asymptomatic patients with chronic AR. In fact, a more marked impairment in both the longitudinal and circumferential strains was already noted at the time of first echocardiography in patients who later required AV surgery compared with patients who did not need surgery on follow-up. This is also consistent with the findings of Olsen *et al.*,[25] who demonstrated that impaired LV longitudinal strain was associated with disease progression or impaired outcomes after surgery in 62 patients with moderate-to-severe AR, although no multivariate analysis was performed in that study. Importantly, the present study showed that either LV longitudinal or circumferential strain provided a significant incremental value over clinical and established echocardiographic predictors of poor outcome, including LV volume and parameters of AR severity (vena contracta width),[1] in predicting those who would require AV surgery. Moreover, when applying the LV longitudinal strain cut-off value of −19.3% (which has a negative predictive value of 100%), it is capable of ruling out the risk of developing indications for AV surgery and thus, watchful waiting should be recommended. Accordingly, LV longitudinal strain may be viewed as a sensitive marker for detection of subtle myocardial changes and may serve as a potential screening tool in clinical risk stratification of asymptomatic patients with chronic moderate-to-severe AR and preserved LVEF. It has the ability to identify those at risk, when the longitudinal strain was more impaired, in whom more aggressive follow-up and early intervention should be considered.

We acknowledge that, due to the relatively small population, the present study should be considered as a hypothesis-generating study to examine the ability of LV strain in the prediction of AV surgery. Additional prospective studies including a larger patient population are warranted to further validate the usefulness of LV longitudinal strain for accurately predicting the need for AV surgery in asymptomatic AR patients with preserved LVEF.

Conclusions

Multidirectional LV strain was more impaired in patients with moderate-to-severe or severe AR who had symptoms than those without symptoms, although LVEF was still preserved. Furthermore, subtle impairment in myocardial function, detectable with 2D-STE, can be used to identify asymptomatic patients who progress to require AV surgery during follow-up.

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Part II

Role of multimodality imaging in transcatheter aortic valve implantation – from screening to outcomes

4

Role of computed tomography imaging for transcatheter valvular repair/insertion

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Role of computed tomography imaging for transcatheter valvular repair/insertion

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Abstract During the last decade, the development of transcatheter based therapies has provided feasible therapeutic options for patients with symptomatic severe valvular heart disease who are deemed inoperable. The promising results of many nonrandomized series and recent landmark trials have increased the number of percutaneous transcatheter valve procedures in high operative risk patients. Pre-procedural imaging of the anatomy of the aortic or mitral valve and their spatial relationships is crucial to select the most appropriate device or prosthesis and to plan the percutaneous procedure. Multidetector row computed tomography provides 3-dimensional volumetric data sets allowing unlimited plane reconstructions and plays an important role in pre-procedural screening and procedural planning. This review will describe the evolving role of multidetector row computed tomography in patient selection and strategy planning of transcatheter aortic and mitral valve procedures.

Keywords Transcatheter heart valve implantation · Computed tomography · Imaging

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Introduction

During the last decade, the development of transcatheter based therapies has provided feasible therapeutic options for patients with symptomatic severe valvular heart disease who are deemed inoperable. The promising results of many nonrandomized series and recent landmark trials, such as the PARTNER trial with the Edwards SAPIEN transcatheter aortic valve prosthesis (Edwards Lifesciences, Irvine, CA, USA) or the EVEREST II trial with the MitraClip device (Abbott Vascular, Structural Heart, Menlo Park, CA, USA), have increased the number of percutaneous transcatheter valve procedures in high operative risk patients [1, 2].

In contrast to open heart surgery where direct inspection of the valve is possible, the decision for device/prosthesis selection and planning of the percutaneous procedure is mainly based on pre-procedural imaging of the anatomy of the aortic or mitral valve and their spatial relationships. These data are usually acquired using 2-dimensional (2D) imaging modalities such as conventional echocardiography and/or invasive angiography. However, 2D echocardiography imaging relies on geometrical assumptions that may reduce the accuracy of the measurements while fluoroscopy has limited soft-tissue resolution. In contrast, advanced cardiovascular imaging modalities such as multidetector row computed tomography (MDCT), provide detailed information on the aforementioned anatomy. MDCT, which has the advantage

of 3-dimensional (3D) volumetric data sets allowing unlimited plane reconstructions, plays an important role in pre-procedural screening and procedural planning with the aim of minimizing procedural-related complications. This review will describe the evolving role of MDCT in patient selection and strategy planning of transcatheter aortic and mitral valve procedures.

Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) has emerged as an effective alternative in high risk patients with symptomatic severe aortic stenosis (AS). Recently, this percutaneous intervention has demonstrated superior survival at 1 year over standard therapy (69.3% vs. 49.3%, with an absolute 20% increase with TAVI procedure) in a selected group of patients with AS who were deemed not suitable for aortic valve surgery [1]. In addition, a recent review involving more than 2,000 patients receiving TAVI reported an implantation success of 94% and a 30-day survival rate of 89% [3]. Accurate assessment of the anatomy of the peripheral arteries and aorta, together with the anatomy of the aortic valve, aortic annular and root dimensions, are the key determinants of procedural feasibility and safety.

Pre-procedural patient evaluation

The multidisciplinary pre-procedural evaluation of patients who are candidates for TAVI includes the assessment of the aortic valvular complex, including the aortic valve and aortic root (for determination of anatomical suitability and prosthesis sizing), and the anatomy of the peripheral arteries and aorta (for determination of the access site) (Table 1).

First, assessment of the aortic valve should begin with confirmation of the *aortic valve morphology*. Usually, this can easily be identified from the short-axis view on transthoracic echocardiography, which remains the initial modality of choice to assess the aortic valve pathology and its hemodynamic consequences [4]. However, in patients with poor acoustic windows and/or in the presence of heavy calcification, differentiating tricuspid from bicuspid valvular anatomy may be challenging [5]. This information is important before the procedure as it is currently not recommended to perform TAVI on bicuspid valves due to the potential risk of an unfavorable deployment [6, 7]. In a recent study of 50 patients with AS (17 bicuspid and 33 tricuspid) [8], transthoracic echocardiography was unable to identify the anatomy of the valve in 10 patients (20%) due to extensive calcification. In contrast, MDCT was able to provide direct visualisation of the aortic valve and thus could correctly identify the valve anatomy in 49 of 50 cases (98%) [8]. Furthermore, the accuracy of the patient selection process can be further improved with additional systolic reconstruction using ECG-gating, which permits differentiation between a bicuspid valve with raphe and a tricuspid valve [9].

Next, the assessment of the extent and location of the *aortic valve calcification* is important before the TAVI procedure. With high spatial resolution and the possibility of direct visualization of the aortic valve, MDCT allows detailed analysis of the quantification and localization of aortic valve calcification (Fig. 1). Several studies [10–12] have indicated the significance of aortic valve calcification and its specific location, as assessed by MDCT, in relation to the presence of post-procedural aortic regurgitation. For example, in a study of 100 patients who underwent TAVI with self-expandable devices, John et al. [11] demonstrated a strong linear correlation ($r = 0.86$, $P < 0.001$) between the degree of aortic regurgitation immediately post-TAVI and the severity of calcification in the device "landing zone", defined as the area extending from the left ventricular outflow tract to the aortic valvular cusps. Similar findings were reported in a series of 53 patients undergoing TAVI [10] whereby moderate post-procedural aortic regurgitation following the implantation of balloon-expandable valves was found in patients who exhibited more calcification of the native aortic valves, especially at the valve commissures (Fig. 1). It has been suggested that bulky calcification may pose resistance during the deployment of the prosthesis, resulting in paravalvular leakage arising from the gap between the prosthesis and the native valve [13]. In addition, very bulky calcification at the edge of native valvular leaflets has been related to increased risk of coronary occlusion when it is displaced over the coronary ostium [14]. Furthermore, TAVI has to be performed with caution when there is heavy calcification in the sinotubular junction as it may cause restriction during balloon expansion at the aortic end,

Table 1 Evaluation before transcatheter aortic valve implantation: anatomic requirements of the currently available prosthesis

Anatomy	CoreValve revalving system		Edwards SAPIEN XT	
	26 mm	29 mm	23 mm	26 mm
Peripheral arteries and aorta				
Iliofemoral artery diameter (mm)	≥6 (18 Fr)		≥6 (18 Fr)	≥6.5 (19 Fr)
Tortuosity				
Calcification				
Aortic valve				
Anatomy				
Calcification				
Annular diameter (mm)	20–23	24–27	18–22	21–25
Aortic root				
Sinus of Valsalva diameter (mm)	≥27	≥28	NA	
Sinotubular junction diameter (mm)	≤40	≤43	NA	
Ascending aorta diameter (mm)	≤43		NA	
Height of the coronary ostia from the aortic annular plane (mm)	≥10		≥8	
Left ventricular septal thickness (mm)	<17		NA	
Coronary artery anatomy	Not in severe proximal coronary lesions not amenable to revascularization		Not in severe proximal coronary lesions not amenable to revascularization	
Intracardiac thrombus	Absent		Absent	

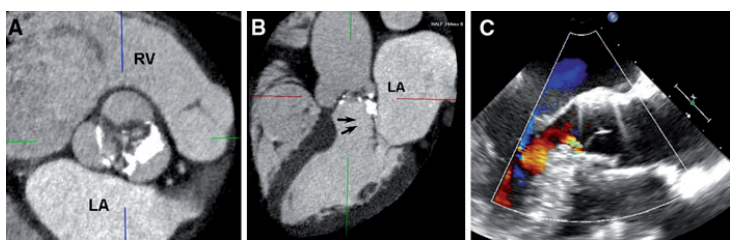

Fig. 1 Aortic valve calcification assessed using multidetector row computed tomography (*MDCT*): implications for transcatheter aortic valve implantation. **a** shows a calcified tricuspid aortic valve with bulky calcification mainly in the *left* cusp, *left–right* commissure and extending to the base of the anterior mitral valve leaflet (indicated by *arrows* in **b**). Following TAVI, paravalvular leak was observed with colour Doppler transesophageal echocardiography in the long-axis view (**c**) that coincided with the location of bulky calcification at the *left–right* commissure on MDCT (in **a**). In this example, the bulky calcified cusp and commissure might pose resistance during transcatheter prosthesis deployment, resulting in subsequent paravalvular leak (arising from the gap between the prosthesis and native valve). *LA* left atrium, *RV* right ventricle

causing ventricular displacement of the device at the time of deployment [15]. Hence, appreciation of the extent and location of calcification, more precisely measured using MDCT, may help to anticipate and thus avoid potential procedural complications.

Besides its implications on the procedural outcome of TAVI, the assessment of aortic valve calcification can be a useful adjunct in the evaluation of AS severity during pre-procedural screening [16, 17]. In a recent study, the degree of aortic valve calcification

measured using MDCT was highly correlated with the hemodynamic severity of AS measured using echocardiography [16].

Accurate evaluation of the *aortic valve annular dimension* is key for appropriate selection of prosthesis size. This process is unique in percutaneous procedures as direct inspection of the valve is not possible. Currently, the Edwards SAPIEN XT device is available in two sizes: 23 mm valve for aortic annulus between 18 and 22 mm and 26 mm valve for aortic annulus between 21 and 25 mm. Similarly, the Medtronic CoreValve system has two sizes: 26 mm valve for aortic annulus between 20 and 23 mm and 29 mm valve for aortic annulus between 24 and 27 mm (Table 1) [18]. This step is critical as inaccurate sizing will result in undesirable periprocedural consequences such as prosthesis migration, significant aortic regurgitation (if undersized) or rupture of the aortic root (if oversized). In most centers, the measurement of the aortic annular diameter is performed using 2D echocardiography. In clinical practice, it is widely recognised that the aortic annulus is defined at the lowest attachment point of the aortic valve leaflets within the left ventricle (LV), forming a virtual ring [19]. As previously shown, this functional ring is not circular but oval in shape (Fig. 2), and is more accurately visualized with 3D imaging techniques [20, 21]. In a recent study of patients undergoing open aortic valve surgery, Smíd et al. [22] compared pre-operative measurements of the aortic annulus using MDCT, magnetic resonance imaging (MRI) and 2D transesophageal echocardiography. Using intra-operative direct measurement as the reference, the accuracy of pre-operative measurement using either MDCT or MRI were superior compared to echocardiographic measurement, highlighting the high precision achievable with MDCT [22]. This is partly due to the high spatial resolution of MDCT which permits improved visualization of the aortic valve. Another explanation is that the anatomical planes of measurement obtained with different modalities are not identical [23, 24]. For example, the parasternal long-axis view for transthoracic or transesophageal echocardiography represents an oblique cut through the aortic annulus and provides a single annular dimension that usually does not correspond to a true anatomical diameter measurement (either the maximum or minimum diameter visualised on MDCT) (Fig. 2).

Given that the aortic annulus is oval in shape, only 3D imaging techniques can provide the most accurate assessment of the aortic annulus dimension. As such, MDCT permits reconstructions in unlimited planes, allowing multiple measurements of the aortic annulus: minimum (D_{min}), maximum (D_{max}), mean ($D_{mean} = [D_{min} + D_{max}]/2$) diameters and cross-sectional areas (Fig. 2) [21, 25]. Depending on how the aortic annulus is measured, the selection of the prosthesis size may differ. For example, in a recent study of 75 patients with severe AS undergoing MDCT as part of procedural planning for TAVI, Schultz and co-workers [25] showed that ineligibility for the currently available Medtronic CoreValve system differed substantially if D_{min} or D_{max} were used. Thus, 26 or 39% of patients would not qualify for TAVI with Medtronic CoreValve system due to too small or too large annular dimensions, respectively. In 50 patients who subsequently received the Medtronic

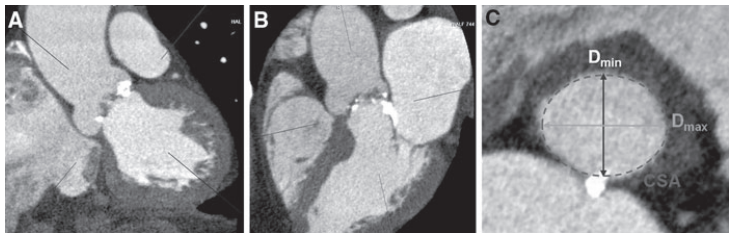

Fig. 2 Aortic valve annular dimensions. Multidetector row computed tomography (*MDCT*) permits excellent visualization of the oval-shaped aortic annulus with correct alignment of the orthogonal multiplane reformation planes (**a** and **b**). The correct aortic annular plane is defined at the lowest attachment point of all the three valve leaflets (**c**) and multiple measurements of the aortic annulus can be made: minimum (D_{min}), maximum (D_{max}), mean ($D_{mean} = [D_{min} + D_{max}]/2$) diameters and cross-sectional areas (*CSA*)

CoreValve prosthesis, the sizing based on D_{mean} had the best agreement with the operator choice ($n = 37$, 74%), whereas the agreement with the operator choice was only 44 or 32% if D_{min} or D_{max} were used, respectively [25]. For the Edwards SAPIEN prosthesis, Messika-Zeitoun et al. [26] reported that using D_{mean}, as measured by MDCT, would have changed the prosthesis size in 38% of patients. Prospective studies examining the value of different imaging modalities in sizing of prosthesis and its immediate impact on procedural outcomes are lacking but are important to establish the gold standard methodology to size the aortic valve annulus and select the prosthesis size.

In addition, the assessment of the *dimensions of the sinus of Valsalva, sinotubular junction and ascending aorta* is an essential step in the pre-procedural evaluation. Using the "center-line approach" and reformations of the aortic root and ascending aorta, MDCT permits accurate measurement of these dimensions. This information is critical especially in patients undergoing the self-expandable device implantation as a dilated aortic root/ascending aorta is currently a contraindication (Table 1) [6].

Next, the 3D analysis of MDCT permits comprehensive and detailed evaluation of the spatial relationship of the aortic valve with the surrounding structures. In particular, the information on the *height of the coronary ostia relative to the aortic annular plane* is important to ensure patency of the coronary arteries following ballooning and deployment of the transcatheter prosthesis (Fig. 3). Currently, a minimum distance of 10 mm is recommended for both devices [18]. In addition, MDCT is an ideal modality to measure the length of the valvular leaflets as it can potentially increase the risk of coronary occlusion, notably in patients with bulky calcification of the aortic leaflets (Fig. 3b) [14]. However, this requirement may vary from individual to individual as the final position of the prosthesis depends on the interaction between the prosthesis and the aortic annulus [15].

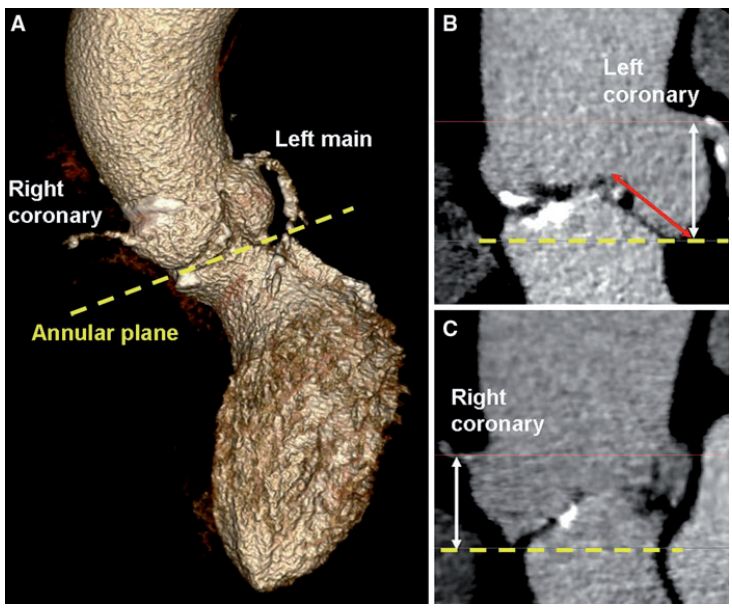

Fig. 3 Assessment of the height of the coronary ostia relative to the aortic annular plane. Multidetector row computed tomography (*MDCT*) permits accurate orientation of the aortic annular plane (**a**) and precise measurement of the distance between the *left* and *right* coronary ostia and the annular plane (**b** and **c**). In addition, the length of the valvular leaflet, measured from the aortic annulus to the cusp tip, can be obtained on MDCT (*red arrow* in **b**)

Finally, evaluation of the *peripheral access artery and aortic anatomy* is fundamental to plan the procedural strategy: retrograde (through a transarterial approach, transfemoral or transsubclavian) or antegrade (through a transapical approach). Although recent advances have allowed for a lower crimped profile delivery device, the transfemoral approach for self- or balloon-expandable systems can only be considered when the minimal diameter of the iliofemoral vessel is $\geq$6 mm (to accommodate a 18F sheath size) [27]. As adequate access is one of the most important determinants of procedural success [28], the decision for selecting the transfemoral approach relies on the *precise measurement of vessel dimension*, *tortuosity* and *calcification of the peripheral arteries and aorta* [6]. In the recent multicenter SOURCE registry of 1,038 patients who received a balloon-expandable prosthesis, the rate of vascular complications with the transfemoral approach was higher (22.9% vs. 4.7%) when compared with the transapical approach, highlighting the need for careful patient selection, to select the most suitable procedural approach to avoid procedural-related vascular complications [29].

Although conventional angiography is the reference method to assess the luminal diameter, tortuosity and calcification of the peripheral arteries and aorta [6], true cross-sectional diameters and areas are better visualized on MDCT. Typically, the curved multiplanar reformation planes (MPR), using the "center-line approach", permits reconstruction of the curved planes, following the course of the vessel regardless of its tortuous course. Ideally, the precise measurement of the vascular structures should be obtained from the axial view, perpendicular to the long axis of the vessel (Fig. 4c, d). In the presence of calcification, the blooming effect has to be brought to a low level when these measurements are being performed.

With the 3D volume rendering images, current MDCT techniques permit rotation and display to best define the total number and severity of angulations along the vessel of interest. Post-processing imaging software is available to detect all angulations along the vessel automatically and allows precise measurement of the severity of angulations (Fig. 4e), which helps to systematically quantify the extent of tortuosity in patients who are being considered for a transfemoral procedure. In addition, MDCT can accurately delineate the location and the extent of calcification along the vessel. This is particularly important in case of a tortuous vessel as significant calcification does not allow straightening of the vessel during advancement of the sheath and should prompt the consideration of an alternative access (either the transapical or transsubclavian approach). Furthermore, severe calcification at the bifurcation of the iliac vessels may become a concern for the transfemoral approach as it may restrict sheath advancement and increase the risk of vessel perforation or dissection. In a recent study by Kurra et al. [30] that examined 100 patients who were considered for TAVI, as many as 35% of patients had unsuitable iliofemoral anatomy defined as one of the following: minimal diameter of the iliofemoral vessel $<$8 mm (a requirement for the older generation delivery system), $>$60% circumferential calcification at the external-internal iliac bifurcation or severe angulation $<$90°. Among those with MDCT criteria of unsuitable anatomy ($n = 35$), 5 patients proceeded with transfemoral-TAVI. Of these 5 patients, 2 (40%) had vascular complications requiring surgical intervention [30].

Besides the anatomical requirement of the iliofemoral arteries, the pre-procedural *assessment of the aorta and its lumen* is necessary as it may guide the approach of TAVI. Presence of bulky atherosclerosis of the aorta, a porcelain aorta, a transverse course of the ascending aorta or a previous aorto-femoral bypass is a contraindication for the transfemoral approach [6]. Fluoroscopy, commonly used to evaluate the luminal diameter of the peripheral arteries, does not allow accurate assessment of arterial wall disease or atherosclerotic plaques. In contrast, MDCT provides a comprehensive evaluation including arterial luminal diameter and wall assessment. The presence of extensive aortic atherosclerosis as detected with MDCT may preclude the transfemoral approach due to the increased risk of cerebrovascular events during manipulation of the catheters along the diseased aorta.

Although suitable vessel anatomy is the key consideration in the transfemoral approach, other aspects need to be considered, which may favour one approach over another. For instance, pericardial calcification, a deformed chest wall anatomy or severe pulmonary disease may make the transapical approach unsuitable and MDCT is helpful to provide such information.

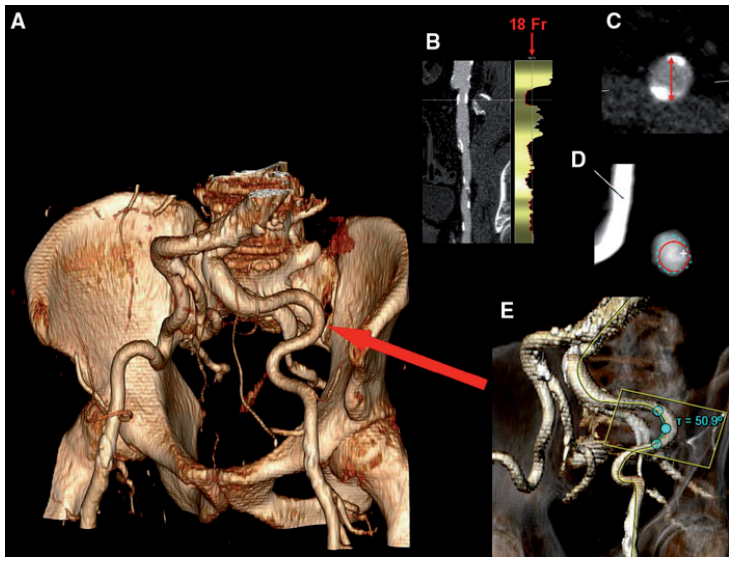

Fig. 4 Evaluation of peripheral arteries with multidetector row computed tomography (*MDCT*). **a** shows an example of infrarenal aorta, iliac and femoral arteries in a 3-dimensional volume rendering view. Using the center-line approach, the curved multiplanar reformation (*MPR*) permits reconstruction of the curved planes, following the course of the vessels. Subsequently, the true cross-sectional internal diameter and area of the iliac artery can be measured from the double oblique transverse view in (**c** and **d**). With the current MDCT post-processing imaging software (3mensio Valves™, version 4.2., 3mensio Medical Imaging BV, Bilthoven, The Netherlands), the minimum diameter threshold required for the currently available transfemoral devices is 6 mm (18 Fr) and this minimum requirement is simultaneously displayed side-by-side in the curved MPR views (**b**). Therefore, the presence of a minimal luminal diameter of the iliofemoral arteries <6 mm does not favor the transfemoral approach. In contrast, the example in **d** shows a vessel with a minimal luminal diameter >6 mm, as indicated by the dotted green circle which is larger than the size of a simulated 18 Fr sheath (in *solid red circle*). In addition, the 3-dimensional reconstruction volume rendering technique of MDCT allows rotations and displays the tortuous course of the iliofemoral arteries. **e** gives the precise measurement of one of the angulations seen in the left external iliac artery (51°), rendering it unsuitable for the transfemoral approach

Planning of interventional access planes

Pre-operative CT has been demonstrated to accurately predict the location of the aortic valve and ascending aorta relative to the chest wall in patients undergoing a minimally invasive approach for aortic valve replacement [31]. Several groups have reported that 3D data obtained from MDCT can help to predict the fluoroscopic projections that are optimal for TAVI procedures [32–34]. An ideal angiographic plane (the so called "implanter's view") should be the projection that aligns all three aortic cusps in a straight line, perpendicular to the aortic valve plane (Fig. 5) [15]. A recent study by Gurvitch et al. [32] compared 2 groups of patients who underwent TAVI with (20 patients) and without (20 patients) pre-procedural MDCT. When MDCT information was available to guide the fluoroscopic projection angle, an excellent or satisfactory final implant projection was achieved in 90% of cases ($n = 18$), as compared to only 65% of cases ($n = 13$) when pre-procedural MDCT was not available [32].

With regard to the transapical approach, the relation of the LV apex and the aortic annulus plane (the so called "ventriculo-aortic angle") can be important (Fig. 6). Recently, the first-in-man series of a new self-expanding prosthesis implantation via the transapical approach was reported in 30 patients [35]. The initial experience highlighted the importance of this ventriculo-aortic angle, which may pose as a challenge during the introduction of a straight and rigid delivery system (via the LV apex) which

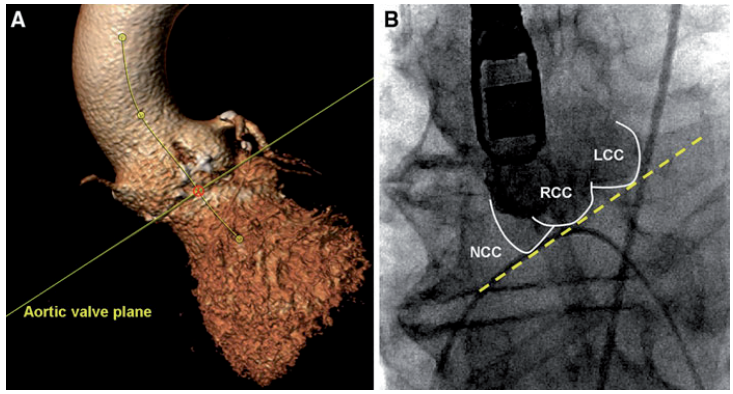

Fig. 5 Planning of angiographic planes. Using reformation reconstruction of multidetector row computed tomography (*MDCT*), the appropriate aortic valve plane for transcatheter aortic valve implantation can be anticipated (**a**). The ideal angiographic projection should be one that aligns all the three aortic cusps in a straight line, perpendicular to the aortic valve plane (**b**). *LCC* left coronary cusp, *NCC* non-coronary cusp, *RCC* right coronary cusp

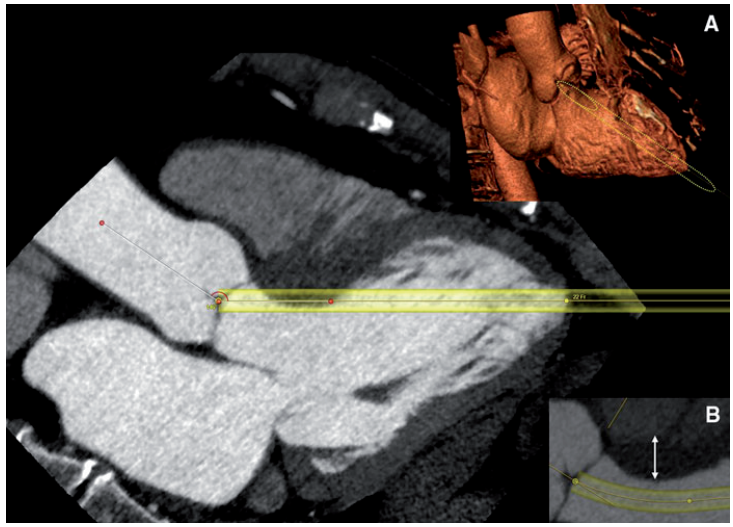

Fig. 6 Assessment of the left ventricular geometry may be of relevance in the planning of the transapical approach. The relation of the *left* ventricular apex and the aortic annulus valve plane (the so called "ventriculo-aortic angle") can be reliably measured on multidetector row computed tomography (*MDCT*). Insert **a** shows the direction of a simulated delivery system through the *left* ventricular apex, towards the aortic valve. In addition, the thickness of the *left* ventricular septum wall can be measured on MDCT (*arrow* in insert **b**). Post-processing imaging software (3mensio Valves™, version 4.2., 3mensio Medical Imaging BV, Bilthoven, The Netherlands)

may not be able to conform to this angle, subjecting patients to a risk of aortic dissection when the device is advanced into the ascending aorta [35]. Novel 3D based post-processing imaging software is currently available to permit direct visualization of this ventriculo-aortic relationship to aid in the planning for the

transapical approach. This allows the anticipation of the angulation required during insertion of the apical sheath and the delivery system, towards the direction of the aortic valve and the ascending aorta (Fig. 6). In addition, the measurement of the LV septal wall thickness with MDCT is important (Fig. 6b) as the presence of severe sigmoid basal septum may prevent stable positioning of the deployed prosthesis (Table 1).

Other factors to be considered before TAVI

In addition to the aforementioned considerations, additional factors need to be evaluated before TAVI, which completes the pre-procedural screening. The evaluation of *coronary artery anatomy* is mandatory as the presence of significant coronary artery disease needs to be revascularized. Current position statement does not recommend TAVI in patients with severe proximal coronary stenoses not amenable to percutaneous coronary interventions [6]. Although MDCT has shown its diagnostic accuracy in the evaluation of coronary artery disease [36], the prevalence of coronary atherosclerosis in the elderly population may limit its accuracy in detecting significant coronary artery stenoses. Therefore, invasive coronary angiography remains the reference modality to evaluate the coronary anatomy in this highly selected group of patients [6].

Finally, LV dimensions, function and the presence of concomitant mitral regurgitation (MR) need to be evaluated before TAVI. This information is usually available from the standard echocardiography, which is still the initial imaging modality in patients scheduled for TAVI. However, in patients with poor acoustic window, MDCT allows assessment of LV dimensions and function using ECG-gating. More importantly, it permits detection of intracardiac thrombus, which is an established contraindication for TAVI (Table 1) [6].

Transcatheter mitral valve repair procedures

Mitral valve repair is the treatment of choice for patients with symptomatic MR [4]. Advances in surgical techniques have led to improved clinical results in young and elderly patients [37]. However, associated comorbidities and low LV ejection fraction increase the operative morbidity and mortality risks in the elderly population and may lead to non-referral or denial for surgery in as many as 50% of the patients with symptomatic severe MR [38].

Transcatheter-based and minimally invasive surgical therapies have been developed over the last years. Several therapeutic options are now available for patients with symptomatic severe MR and high operative risk. These percutaneous techniques can be classified as leaflet-based (edge-to-edge repair, Mitraclip device [Abbott Vascular, Structural Heart, Menlo Park, CA, USA]), coronary sinus or mitral annulus-based (Carillon, Monarc or Viacor devices and Quantum cor and Mitralign devices, respectively) and LV-based (Coapsys device [Myocor, Maple Grove, MN]). The EVEREST II trial has shown the feasibility, safety and efficacy of the Mitraclip device in reducing MR and improving clinical symptoms [39]. In addition, initial experiences with devices designed to reduce the mitral annulus perimeter and improve the mitral leaflet coaptation (the AMADEUS and the EVOLUTION trials) demonstrated that transcatheter mitral restrictive annuloplasty approaches may be a feasible alternative to surgery in selected patients [40–42]. Furthermore, the results of the RESTORE-MV trial showed that patients with functional MR benefited from ventricular reshaping with the Coapsys device, with significant improvement in clinical symptoms and survival [43].

The feasibility and efficacy of these transcatheter-based or minimally invasive surgical therapies rely on the presence of suitable valve and LV anatomy and geometry. Evaluation of the underlying mechanism of MR is crucial to select the most appropriate transcatheter based therapy (Table 2). In brief, MR can be divided into organic or primary MR when the mitral valve itself is diseased (i.e. Barlow's disease, healed infective endocarditis) and secondary or functional MR when the mitral valve is anatomically normal but a remodeled and dysfunctional LV prevents adequate coaptation of the mitral leaflets. Two-dimensional and recently, 3D transesophageal echocardiography are the mainstay imaging techniques used in surgical decision-making (mitral valve repair or replacement). However, the high spatial resolution of MDCT permits accurate assessment of the anatomy, geometry and spatial relationships of the mitral valve complex and thus provides important information for selecting candidates for these therapies.

Table 2 Transcatheter-based mitral valve repair techniques

Mitral valve repair technique	Device	Trial	Indication
Leaflet repair	MitraClip	EVEREST I	Organic mitral valve regurgitation
		EVEREST II	Functional mitral valve regurgitation
Coronary sinus-based annuloplasty	Carillon	AMADEUS	Functional mitral valve regurgitation
	Monarc	EVOLUTION	
	PTMA	PTOLEMY-1	
Direct LV remodelling	Coapsys	RESTOR-MV	Functional mitral valve regurgitation

MDCT before mitral leaflet repair

The Mitraclip device is delivered to the mitral valve via percutaneous femoral venous transseptal puncture and creates a double-orifice valve, resulting in improved mitral leaflet coaptation and MR reduction. After crossing the interatrial septum, the delivery system is steered toward the mitral valve plane and the clip is aligned perpendicular to the mitral leaflets and centered in the area with the largest effective regurgitant orifice area. Afterwards, the delivery system is advanced into the LV and the arms of the clip are opened for subsequent grasping and coaptation of the leaflets at the targeted scallops.

Transesophageal echocardiography plays a central role in pre-procedural screening and procedural guidance during the intervention. Current 3D transesophageal echocardiography permits visualization of the mitral valve from multiple perspectives, orientation of the MPR to localize the largest regurgitant orifice and accurate characterization of the underlying mechanism of MR. Similarly, MDCT enables accurate 3D visualization of the mitral leaflets and detailed evaluation of the anatomic criteria essential in percutaneous Mitraclip implantation:

- Central regurgitant jet, located at the central scallops of the anterior (A2) and posterior (P2) mitral leaflets.
- Coaptation length $\geq$2 mm and coaptation depth $\leq$11 mm (for functional MR).
- flail gap <10 mm and flail width <15 mm (for organic MR).

Multidetector row computed tomography data reconstructed in smaller (such as 5%) increments throughout the RR interval provide high spatial resolution images with improved temporal resolution and enable identification of the systolic frame where mitral leaflet coaptation failure occurs.

In addition, MDCT provides information on the *underlying mechanism of MR*. For example, the diagnostic performance of MDCT to identify mitral valve prolapse was recently evaluated in a series of 53 patients [44]. The orientation of the MPR across the mitral valve plane provides the LV 4-, 2- and 3-chamber apical views and enables localization of the mitral valve prolapse, billowing and flail leaflet (Fig. 7). The sensitivity, specificity, positive predictive value and negative predictive value of MDCT for diagnosis of mitral valve prolapse were 96, 93, 93 and 96%, respectively [44]. Furthermore, the assessment of the *mitral valve geometry* and the measurement of the tenting heights (coaptation depth) and leaflet angles can be accurately performed in patients with functional MR [45]. The orientation of the orthogonal MPR across the modified short-axis view of the mitral valve provides the 4-chamber view at the anterolateral (A1–P1), central (A2–P2) and posteromedial (A3–P3) levels (Fig. 8). In a series of 67 heart failure patients, including 29 patients with significant functional MR, the mitral valve geometry was evaluated with MDCT [45]. In patients with significant MR, the maximum tenting height and tethering of the posterior mitral leaflet were located at the central and posteromedial levels. The knowledge of these data beforehand permits accurate planning of the procedural strategy and may result in a significant shortening of fluoroscopy and procedure timings.

MDCT before coronary sinus annuloplasty

Coronary sinus-based mitral annuloplasty devices have been designed to treat functional MR percutaneously. Two anchors or stents connected by a bridge

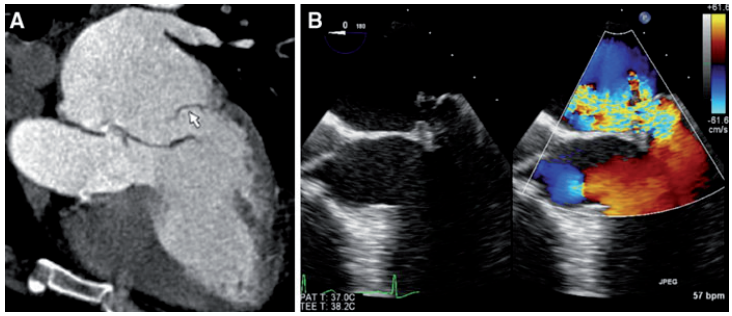

Fig. 7 Evaluation of underlying mechanism of mitral regurgitation with multidetector row computed tomography (*MDCT*). Mitral valve prolapse can be identified accurately with MDCT. **a** shows an example of a patient with prolapse of the posterior leaflet (*arrow*). Color Doppler echocardiography permits quantification of the regurgitant volume and the direction of the regurgitant jet (**b**). Modified with permission from Feutchner et al. [44]

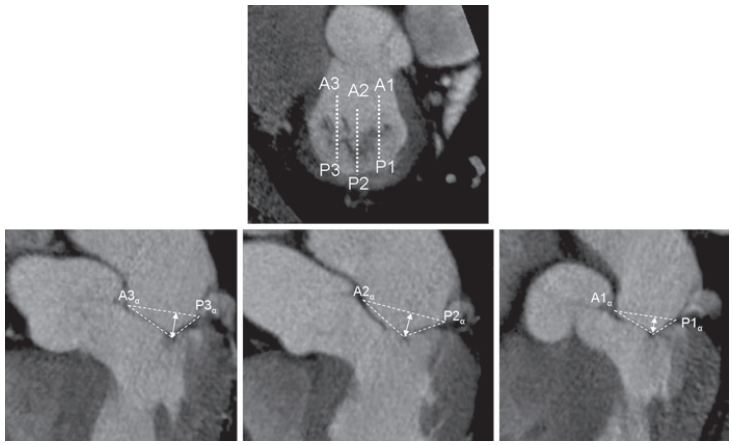

Fig. 8 Mitral valve geometry assessment with multidetector row computed tomography (*MDCT*) in functional mitral regurgitation. From the short-axis view of the mitral valve at the level of the mitral leaflets and commissures, the orthogonal planes across the anterolateral (*A1–P1*), central (*A2–P2*) and posteromedial (*A3–P3*) provide the apical views of the mitral valve apparatus and permits the measurement of the leaflet angles and tenting heights (*arrows*)

element are placed within the distal part of the coronary sinus or the great cardiac vein and in the coronary sinus ostium. The bridging connector constraints the coronary sinus and reduces the anteroposterior diameter of the mitral annulus, improving the coaptation of the mitral leaflets and reducing the MR. Data from the AMADEUS trial have demonstrated the feasibility, safety and efficacy of this therapy [42]. Out of 48 heart failure patients enrolled with significant functional MR, 30 patients received the Carillon device (Cardiac Dimensions, Inc., Kirkland, WA). At 6 months follow-up, significant reductions in regurgitant volume, effective orifice regurgitant area and vena contracta were observed, together with significant improvements in clinical status [40]. However, one of the main concerns of this therapy is the possibility of impingement of the epicardial coronary arteries. In 17% of implants, a significant arterial impingement involving the circumflex coronary artery was observed. In addition, an

insufficient change in MR grade was observed in 4 patients. The variable position and course of the coronary sinus relative to the mitral annulus is one of the determinants of the efficacy of this therapy.

Multidetector row computed tomography provides useful information on the *dimensions of the coronary sinus and its position relative to the mitral annulus and the circumflex coronary artery* [46–48]. Combining the axial views and 3D volume renderings, MDCT permits evaluation of the feasibility and safety of coronary sinus-based mitral annuloplasty procedures (Fig. 9). Tops et al. [47] evaluated the dimensions, course and spatial relationships of the coronary sinus in 105 patients undergoing MDCT. In 90% of patients, the coronary sinus was superior to the mitral valve annulus with a distance that ranged between 1.4 and 16.8 mm. Importantly, this distance was significantly larger in patients with heart failure as compared to controls (6.2 ± 3.4 mm vs. 4.4 ± 3.4 mm, $P < 0.05$). Therefore, in a significant number of patients the coronary sinus coursed along the posterior wall of the left atrium rather than along the mitral annular plane reducing the efficacy of this device to improve MR. In addition, in 68% of

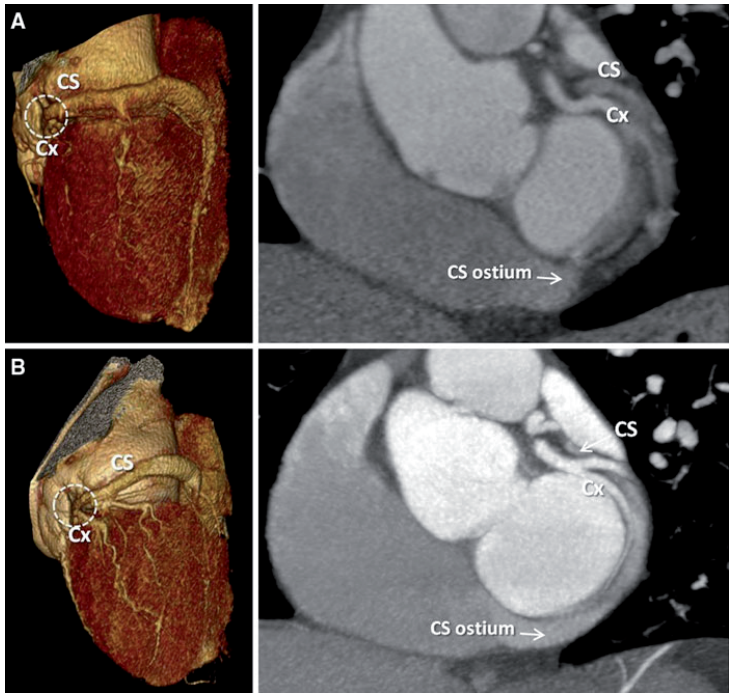

Fig. 9 Multidetector row computed tomography (*MDCT*) prior to coronary sinus-based mitral valve annuloplasty. Combination of 3-dimensional volume rendering and axial views of the mitral valve annulus permit assessment of the key anatomic relationships of the coronary sinus: its position relative to the mitral annular plane and the circumflex coronary artery. **a** shows an example of a patient with the coronary sinus properly aligned with the mitral annulus (as seen with the 3-dimensional volume rendering). However, at the level of the distal part of the coronary sinus, where the distal anchor is positioned, the circumflex coronary artery courses between the mitral annulus and the coronary sinus. The risk of coronary impingement in this example may contraindicate the procedure. In contrast, **b** shows an example where the coronary sinus courses superiorly to the posterior mitral annulus. The coronary sinus-based mitral annuloplasty may be less effective in this case, since the tension is applied to the posterior wall of the left atrium rather than the mitral annulus. In addition, there is a potential risk of circumflex coronary artery compromise as the distal part of the coronary sinus courses over the artery (*arrow*). *CS* coronary sinus, *CX* left circumflex artery

patients, the circumflex coronary artery coursed between the coronary sinus and the mitral annulus, indicating an increased risk of arterial impingement during percutaneous coronary sinus-based annuloplasty. This information can be also obtained with MRI, a valuable alternative to MDCT in patients with severe renal dysfunction in whom the use of iodinated contrast may be contraindicated [49].

MDCT before direct LV remodeling

The RESTOR-MV trial evaluated the efficacy of the Coapsys device (Myocor, Inc., Maple Grove, MN) in reducing MR and improving clinical outcomes of heart failure patients with functional MR undergoing surgical revascularization [43]. This device is placed without the need of cardiopulmonary bypass and aims to reduce the mitral valve annular dimensions and correct the displacement of the papillary muscles. The anterior and posterior pads are positioned on the epicardial surface of the heart and the expanded polytetrafluoroethylene-coated subvalvular cord that connects both pads is tightened under echocardiographic guidance until significant reduction or elimination of MR is achieved [50]. Several anatomic and geometric criteria determine the eligibility for this procedure. Presence of structural abnormality of the mitral valve apparatus (i.e. leaflet prolapse, chordal rupture, mitral annular calcification or calcified leaflets) and LV end-diastolic diameter >70 mm contraindicate this procedure. In addition, the potential interference with the papillary muscles or the inability to avoid main epicardial coronary arteries during device positioning may influence the feasibility of this treatment.

As previously mentioned, MDCT provides accurate characterization of the *LV dimensions, anatomy and location of the papillary muscles and location and extent of mitral valve apparatus calcification* [45, 51]. Furthermore, the position of the anterior and posterior pads can be anticipated during pre-procedural screening, by visualizing the position of the main epicardial coronary arteries in the 3D volume renderings. Compared to the group of patients undergoing surgical coronary artery bypass grafting alone or in combination with mitral valve repair, the RESTOR-MV showed a significant improvement in MR, LV systolic function and survival of patients with ischemic heart failure and functional MR [43].

Conclusions

Accurate selection of patients who are candidates for a transcatheter-based valve repair/implantation technique results in high success rates and reduces the number of procedural complications. MDCT should play a central role in both aortic and mitral transcatheter-based interventions as it provides a comprehensive assessment of the anatomy prior to the procedure and helps to select the most appropriate procedural approach, making the procedure as safe as possible. In addition, the use of state of the art scanners and dose modulation MDCT protocols can potentially optimise the iodined-based contrast load and reduce the radiation exposure.

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Selecting patients for transcatheter aortic valve implantation

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Transcatheter aortic valve implantation (TAVI) is a feasible therapeutic alternative for patients with severe symptomatic aortic stenosis who are considered high risk for surgical aortic valve replacement. The clinical results of TAVI are promising, with over 90% procedural success rates and superior 1-year survival, as compared with medical treatment. Appropriate selection of patients is crucial to optimize procedural success and to minimize the complication rate. A careful multidisciplinary evaluation of clinical symptoms and assessment of aortic valve annular size and dimensions of the peripheral arteries is mandatory to plan the TAVI strategy. Multimodality imaging plays a central role in the preprocedural evaluation of patients who are candidates for TAVI. Patient selection procedure and planning strategy for TAVI will be extensively discussed in the present article.

KEYWORDS: aortic stenosis ▪ clinical assessment ▪ multimodality imaging ▪ TAVI

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Aortic valve replacement (AVR) is the standard treatment for patients with symptomatic severe aortic stenosis (AS) [1,2]. Despite the fact that AVR can improve survival and provide symptomatic relief for these patients, as many as one third of elderly patients with indications for surgery were not operated on [3]. This is at least partly due to the perceived high operative risk associated with a combination of factors including advanced age, multiple comorbidities and/or left ventricular dysfunction. As the survival of unoperated patients with symptomatic severe AS is dismal [4], this has led to the search and development for a less invasive but effective therapeutic alternative for this group of patients, who are deemed unsuitable or have contraindications for surgery.

Since the first successful experience in humans in 2002 [5], transcatheter aortic valve implantation (TAVI) has been rapidly expanding with more than 17,000 procedures performed worldwide to date [6]. Besides the promising procedural success rates of 91–94% observed in recent studies [7–9], a marked improvement in transvalvular hemodynamics [8,10] and functional status have been reported following TAVI [10,11]. More importantly, the results of the first randomized controlled trial (the PARTNER trial) comparing TAVI and standard medical therapy (including balloon valvuloplasty) have demonstrated that TAVI was associated with a superior survival rate at 1 year (69 vs 49%) [12].

Advances in transcatheter technology and its delivery systems over the last few years have helped to improve the clinical results of TAVI resulting in a significant reduction in the 30-day mortality rate (from the initial 14.3 to 6% in the most recent series) [8,9,12–15]. However, there are still several areas of concern, including vascular complications, stroke, atrioventricular conduction block, coronary artery obstruction, prosthesis malpositioning/malfunctioning and paravalvular leakage. Careful patient selection is therefore crucial to minimize procedural complications and optimize the success of TAVI. In this selection process, noninvasive imaging plays a key role in providing information on procedural feasibility and helps to select the most appropriate TAVI approach. This article will describe the steps involved in patient selection (both clinical and anatomic aspects) and TAVI strategy planning.

Clinical risk assessment & evaluation of symptoms

Transcatheter aortic valve implantation is currently restricted to patients with high operative risk for AVR and a life expectancy of ≥1 year, as recommended by a joint position statement from the European Association of Cardio-Thoracic Surgery and the European Society of Cardiology, in collaboration with the European Association of Percutaneous Cardiovascular Interventions [16]. As risk assessment and decision making is a complex process in these elderly patients, a multidisciplinary team approach is essential in making accurate and unbiased clinical assessments on an individual basis [17]. Often, the multidisciplinary team (or so-called 'Heart

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Team') involves the clinical cardiologist, imaging specialist, surgeon, interventionalist, anesthesiologist and geriatrician. To evaluate the risk of surgery, multiple risk scores are available such as the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) [18], the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score [101] or the Ambler score [19]. However, as these risk scores are not designed for isolated AVR, there is a discrepancy between the expected and observed mortality for patients undergoing AVR based on these scoring systems [20–22]. While the widely used logistic EuroSCORE has been shown to overestimate mortality [20,21], the STS-PROM score appears to underestimate but closely approximates the actual observed perioperative mortality for this high-risk group undergoing AVR [20]. As a general guide, several risk scores should be used together to provide a better estimate of the risk involved. The current position statement considers a high-risk patient for surgery when the expected mortality is >20% as calculated with the Logistic EuroSCORE and >10% as calculated with the STS-PROM score [16]. However, owing to the aforementioned limitations, clinical judgment takes precedence over these currently applied scoring systems. In addition, some important factors, which are not reflected in the risk scores, such as chest radiation, porcelain aorta, liver cirrhosis and prior aorto-coronary bypass surgery with patent grafts, may preclude an open heart surgery, and in such cases, TAVI may be the next best therapeutic option [16].

In addition, detailed assessment of comorbidities and physical activity status are an integral part of the pre-procedural screening as these factors have an impact on the life expectancy of the elderly patients [23]. Currently, TAVI should not be performed in patients with a life expectancy <1 year [16]. Moreover, the baseline physical frailty score, as assessed with the Karnofsky index [24], is an independent predictor of in-hospital outcomes following TAVI [7]. Therefore, detailed clinical assessment is critical to ensure that TAVI should be reserved for patients who would derive the maximal benefit from such a procedure.

Next, the evaluation of patients' symptoms is another important aspect of the pre-procedural patient screening. Often, there is a myriad of reasons that may account for the symptoms experienced in the elderly population. At the present stage, TAVI is only recommended for patients with symptoms that are attributed to AS [16]. Thus, a complete clinical assessment may need to involve inputs from other expertise such as those from respiratory physicians and geriatricians in order to be certain that these patients truly have symptoms related to AS before they proceed to TAVI.

Assessment & confirmation of AS severity

Transthoracic echocardiography (TTE) is the initial modality of choice to assess AS as it readily provides information on valve anatomy, transvalvular hemodynamics and left ventricular response to chronic pressure overload state [25]. Quantification of AS severity relies primarily on the hemodynamic parameters, obtained from echocardiographic Doppler measurements (Figure 1A). Severe AS is defined as an aortic jet velocity >4 m/s and/or a mean pressure gradient >40–50 mmHg and/or an aortic valve area <1 cm^2 (or 0.6 cm^2/m^2 indexed to body surface area) [1,2,25]. In the presence of severe left ventricular systolic dysfunction (ejection fraction ≤40%), patients with true severe AS can present with a relatively low transvalvular pressure gradient (<40 mmHg). The diagnosis of this subgroup of patients with 'low flow, low gradient AS' may be challenging and differentiation from other patients with a primary cardiomyopathic disease and a nonstenotic aortic valve (pseudosevere AS) may be difficult [26]. In such cases, dobutamine stress echocardiography should be performed to distinguish between true severe AS from pseudosevere AS [25]. During dobutamine infusion, an increase in transvalvular flow will occur and patients with pseudosevere AS will show an increase in valve area, with little change in transvavular gradient. By contrast, patients with true severe AS will respond by an increase in transvalvular gradient while the aortic valve area remains unchanged [27]. Intervention should be performed in patients with true severe AS who have developed symptoms [1,2].

Evaluation of TAVI feasibility & selection of procedural approach

After confirmation of severe AS and detailed clinical assessment, a comprehensive and accurate evaluation of the feasibility of TAVI is important to ensure the success of the procedure and minimize procedural related complications. Currently, two types of prosthesis are available: the balloon expandable Sapien XT™ prosthesis (Edwards Lifesciences, Irvine, CA, USA) and the self expandable Medtronic CoreValve Revalving™ (MCR) prosthesis (Medtronic Inc., Luxembourg).

The Sapien XT prosthesis is a trileaflet pericardial bovine valve, mounted within a cobalt-chromium frame that permits thinner struts and lower crimped profile. The available sizes are 23 and 26 mm for an aortic valve annulus of 18–22 mm and 21–25 mm, respectively. The 23 mm prosthesis is mounted onto an 18F transfemoral NovaFlex delivery system (Edwards Lifesciences), whereas the 26-mm valve is crimped onto a 19F NovaFlex delivery system. In addition to a retrograde transfemoral approach, this transcatheter aortic valve can also be implanted antegrade via a transapical approach using the 22F Ascendra 2 delivery system (Edwards Lifesciences). Recently, a 29 mm device has been launched for aortic valve annular dimensions between 25–28 mm. This device can be implanted through a transapical approach. The MCR prosthesis has a different design and is characterized by a 50 mm nitinol frame with three different functional levels: the upper third level that exerts a low radial flow and is placed in the ascending aorta; the middle third level that includes the trifoliate porcine valve and has a constraint design to avoid jailing of the coronary ostia; and the lower third level that exerts a high radial force and anchors the prosthesis within the left ventricular outflow tract. In addition, the lowest 12-mm skirt portion helps to prevent significant paravalvular regurgitation after deployment. This prosthesis is currently available in two sizes (26 and 29 mm for aortic valve annulus of 20–23 and 23–27 mm, respectively) and can be implanted via a transfemoral or transsubclavian approach [28]. These different designs and procedural approaches demand accurate evaluation of the aortic valve annulus and peripheral artery anatomy in order to plan the most appropriate therapeutic strategy. Besides these two key aspects, evaluation of the anatomy of the aortic valve, dimensions of the aortic root and its spatial relationship with coronary ostia and exclusion of contraindications complete the pre-procedural evaluation of patients who are candidates for TAVI (Table 1). The use of multimodality imaging is therefore essential to assess these requirements, and to ensure a successful procedure and prevent complications.

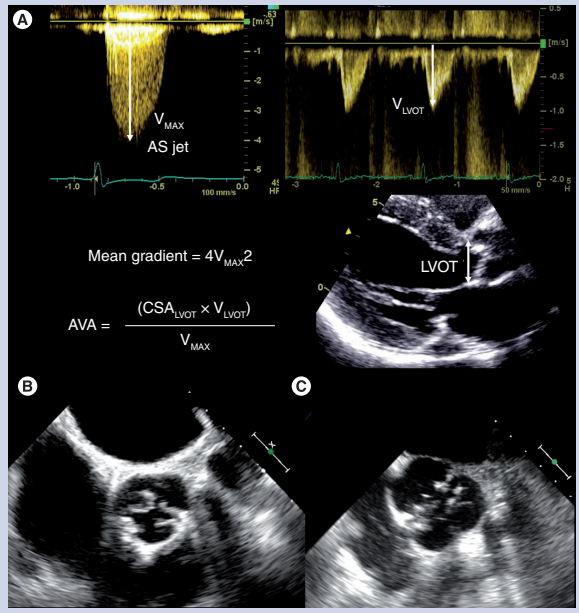

Figure 1. Assessment of the severity of aortic stenosis and aortic valve anatomy. Calculation of mean pressure gradient requires the V_{MAX} of AS jet obtained from continuous-wave Doppler, using the Bernoulli equation **(A)**. Using the continuity equation, AVA is calculated. The LVOT diameter is measured and the CSA_{LVOT} is calculated. In addition, the V_{LVOT} is obtained from pulsed-wave Doppler in the apical long-axis view and the V_{MAX} jet is measured from the continuous wave Doppler recordings through the aortic valve. Either the velocity time integrals or velocities can be applied in the equation for the calculation of AVA.
Transesophageal echocardiography permits direct visualization of the aortic valve: tricuspid **(B)** or bicuspid **(C)**.
AS jet: Aortic jet; AVA: Aortic valve area; CSA: Cross-sectional area; LVOT: Left ventricular outflow tract; V_{LVOT}: LVOT velocity; V_{MAX}: Maximum velocity.

■ Aortic valve anatomy

Transcatheter aortic valve implantation is indicated in patients with a severely stenotic tricuspid aortic valve. The current position statement considers bicuspid aortic valve anatomy as a contraindication for TAVI due to the risk of incomplete and unfavorable deployment [29]. However, several reports have demonstrated that TAVI is a feasible and safe treatment for bicuspid aortic valve [30,31]. Echocardiography remains the mainstay imaging technique to evaluate the anatomy of the aortic valve. However, poor acoustic windows may challenge the diagnosis of this valvular phenotype. Transesophageal echocardiography (TEE) may be an alternative as it provides superior image quality, permitting better visualization of valve anatomy (Figure 1). In addition, multidetector row computed tomography (MDCT) or MRI may help to differentiate truly bicuspid anatomy from functional bicuspid valves [32].

■ Aortic valve calcification

Degenerative aortic valve stenosis is characterized by thickening, retraction and calcification of the aortic valve leaflets. This calcification

Table 1. Anatomic requirements for Sapien XT™ and Medtronic CoreValve Revalving system™ implantation.

Anatomy	Sapien XT	Medtronic CoreValve Revalving system
Anatomical structure		
Annulus (width)	18–22 mm → 23 mm device 21–25 mm → 26 mm device 25–28 mm → 29 mm device	20–23 mm → 26 mm device 24–27 mm → 29 mm device
Annulus-to-aorta (angle)	–	≤45°
Height of sinus of Valsalva	≥15 mm	≥15 mm
Coronary ostia (height) from aortic annulus	≥8 mm	≥10 mm
Ascending aorta (width)	–	≤40 mm → 26 mm device ≤43 mm → 29 mm device

Data taken from [51].

helps to anchor the transcatheter aortic valve prosthesis. However, extensive and bulky calcifications of the aortic valve may challenge deployment of the prosthesis and has been related to the presence of significant postprocedural aortic valve regurgitation [29,33,34]. Fluoroscopy and echocardiography permit gross evaluation of the extent and location of calcification. However, the spatial resolution of MDCT provides improved image quality to evaluate this aspect (Figure 2). Several studies have demonstrated the role of MDCT to evaluate native aortic valve calcification and have related the extent of valve calcification to the presence of paravalvular aortic regurgitation post-TAVI [33,34]. In a recent study by John and coworkers including 100 patients who underwent TAVI, acute post-procedural valvular regurgitation was significantly correlated with the extent of aortic valve calcification in the landing zone [34]. Furthermore, in a series of 53 patients who underwent TAVI, the extent of valve calcification detected with MDCT was significantly higher in patients with non-circular deployment of prosthesis (3862 vs 1837 Hounsfield unit; $p = 0.04$) and significant valvular regurgitation (4174 vs 2444 Hounsfield unit; $p < 0.001$) [33]. Moreover, valve calcification located at the native valve commissures (but not at the valve hinge points or free edge of leaflets) seemed to play a role in determining significant valvular regurgitation following TAVI.

■ Aortic valve annular dimensions

Accurate assessment of the aortic valve annular dimensions is key to select the most appropriate transcatheter prosthesis size. Migration of the

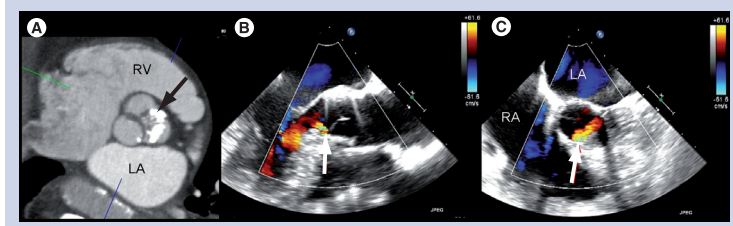

Figure 2. Aortic valve calcification: implication for transcatheter aortic valve implantation.
Multidetector row computed tomography (MDCT) allows assessment of the extent of calcification and its location on the native aortic valve. The photographs shows a tricuspid aortic valve with bulky calcification at the valve commissure (between left and right leaflets) and the body of the left coronary cusp in **(A)**. After transcatheter aortic valve implantation, paravalvular leak (arrow) was observed with color Doppler transesophageal echocardiography in the long-axis view **(B)** and in the short axis view **(C)** that coincided with the location of bulky calcification at the valvular commissure on MDCT (arrow in **(A)**).
LA: Left atrium; RA: Right atrium; RV: Right ventricle.

prosthesis, when the prosthesis size is too small, or rupture of the aortic valve annulus, when the prosthesis size is too large, are two potential procedural complications that can be avoided by accurate measurement of the aortic valve annulus and appropriate sizing of the prosthesis. 2D echocardiography is the most commonly used technique to measure the aortic valve annulus [35,36]. However, 3D imaging techniques have demonstrated that the aortic valve annulus is not circular, but oval shaped (Figure 3A). Currently, the gold standard imaging technique for the measurement of aortic valve annulus has not been established. However, several studies have demonstrated the superior accuracy of 3D imaging techniques to assess this functional structure [37]. In a recent series of 53 patients undergoing TAVI, the accuracy of 2D and 3D TEE to measure the aortic valve annulus was evaluated, using MDCT as the gold standard [38]. Circular areas calculated with 2D and 3D TEE significantly underestimated the planimetered cross-sectional areas obtained with MDCT (16.4 and 12.9% underestimation, respectively). By contrast, planimetered areas of the aortic valve annulus, measured with 3D TEE, had better agreement with MDCT planimetered cross-sectional areas and the percentage of underestimation was significantly lower (9.6%). Although the clinical implications of these different evaluations have not been fully elucidated, 3D imaging techniques such as 3D TEE or MDCT may be helpful in patients with borderline aortic annular measurement. In a recent study including AS patients who underwent MDCT prior to TAVI with MCR prosthesis, Schultz *et al.* demonstrated that prosthesis sizing based on the mean annular diameter ([minimal diameter + maximal diameter]/2) obtained from MDCT had the best agreement with the operator choice (74%) [39]. By contrast, the agreement with the operator choice was only 44 or 32% if only the minimal diameter or maximal diameter was used, respectively. Similarly, the study by Messika-Zeitoun *et al.* reported that using the mean annular diameters measured by MDCT would have changed the prosthesis size in 38% of patients who received Edwards Sapien™ prosthesis [35]. These findings suggest the clinical relevance from incorporating detailed anatomy assessment of the aortic annulus with 3D imaging modalities such as that of 3D TEE or MDCT or MRI.

■ Assessment of aortic root anatomy

In addition to the measurement of the aortic valve annular diameter, the dimensions of the sinus of Valsalva, sino-tubular junction and ascending aorta should be assessed (Figure 3B). Particularly, the dimensions of the aortic root and the ascending aorta are of importance when a MCR prosthesis is implanted. The distal part of this prosthesis accommodates these two anatomical structures, exerting a low radial force and orienting the prosthesis in the direction of blood flow. Dilated ascending aorta (>43 mm) are considered contraindications for self-expandable prostheses (Table 1) [16].

Furthermore, measurement of the height of the coronary ostia, relative to the aortic valve annular plane, is important in order to anticipate

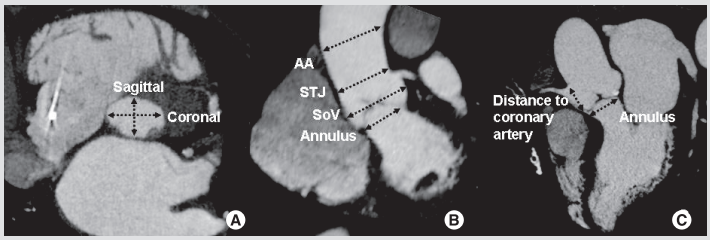

Figure 3. Multidetector row computed tomography assessment of the anatomy of aortic annulus and its surrounding structure. (A) Shows the cross-sectional area of the aortic annulus demonstrating the oval-shaped structure. The sagittal diameter of the aortic annulus is shorter than the coronal diameter. **(B)** Shows the oblique transverse view of multiplanar reformation (MPR) measuring the diameter of AA, STJ, SOV and the coronal aortic annulus diameter. The distance of SOV and coronary cusps from the aortic annulus can be derived. **(C)** Shows the sagittal view of MPR measuring the sagittal diameter of the aortic annulus resembling measurement from echocardiography and distance to the right coronary artery from aortic annulus.
AA: Ascending aorta; SOV: Sinus of Valsalva; STJ: Sinotubular junction.

potential fatal complications such as occlusion of one of the coronary ostia by a bulky calcified cusp [40,41]. The design of the current prostheses, with open struts in the upper two-thirds of the frame, assures normal flow through the coronary ostia. In particular, the MCR device has a constrained middle part, to avoid jailing of the coronary ostia. By contrast, the Sapien XT device seldom reaches the coronary ostia (11% in a recent series) [33]. A coronary ostia height relative to the aortic valve annular plane of at least 10 mm is currently the recommended minimum height to proceed with the procedure (Figure 3C). These characteristics are best evaluated with MDCT, providing a 3D visualization and accurate measurement.

■ Assessment of the aorta & peripheral arteries

Once the prosthesis size has been selected, the procedural approach (retrograde or antegrade) has to be planned. The retrograde approach via the transfemoral access is usually the approach of first choice. In this aspect, the dimensions of the ilio-femoral arteries will directly determine the feasibility of this procedural approach as the currently available devices require a minimum diameter of at least 6 mm. Traditionally, conventional angiography was considered the gold standard method to assess the dimensions of the ilio-femoral arteries. However, the poor soft-tissue resolution of this imaging technique does not allow accurate assessment of arterial wall disease and calcification. MDCT has demonstrated its superior accuracy to assess the internal diameter of the arterial lumen, the presence of significant atherosclerosis and calcification and the tortuosity of the arteries. These are the crucial determinants of success and feasibility of the transfemoral approach (Figure 4) [42,43]. In a recent series including 37 patients undergoing TAVI, it was demonstrated that MDCT had a high accuracy to evaluate the anatomy of the peripheral arteries, with the advantage of using a lower volume of iodinated contrast compared with invasive angiography [42]. In addition, a

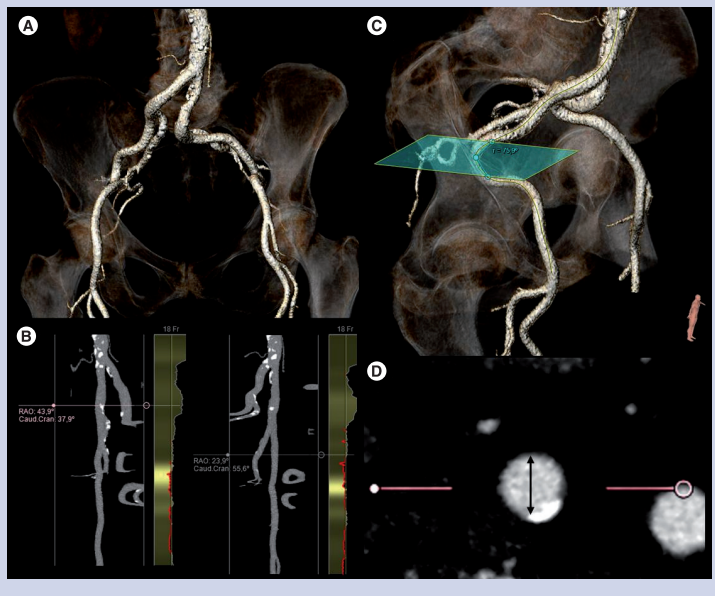

Figure 4. Evaluation of peripheral arteries with multidetector computed tomography.
(A) Shows an example in volume-rendered image, highlighting the tortuous course of the vessel. Using the center-line approach, the distribution of calcification along the vessel (stretched view in **(B)**) and the internal luminal diameter of the vessel (double oblique transverse view in **(D)**) can be accurately assessed. In addition, the exact angulation within the artery can be measured on the volume-rendered image with multidetector computed tomography **(C)**. Post-processing imaging software: 3mensio Valves™, version 4.2., 3mensio Medical Imaging BV, Bilthoven, The Netherlands.

new sequence of magnetic resonance angiography, the true-fast imaging with steady-state precession (a hybrid T2/T1-weighted acquisition), provides excellent visualization of vessels without the need for a paramagnetic contrast agent such as gadolinium (Figure 5) [44].

Evaluation of the aortic arch and descending aorta is also of importance when a transfemoral approach is considered. According to current recommendations, severe angulation of the aorta, severe atherosclerosis of the arch, and coarctation and aneurysm of the abdominal aorta with protruding mural thrombosis contraindicate the transfemoral approach. Severe atherosclerosis of the descending aorta and aortic arch can be detected with TEE (Figure 5). In addition, intravascular ultrasound permits characterization of atherosclerotic plaque [45]. MDCT provides 3D visualization of the aorta and is the method of choice to evaluate the presence of extensive calcification (porcelain aorta). Moreover, MRI provides accurate assessment of the aortic wall without need for paramagnetic contrast. Presence of severe aortic atherosclerosis indicates the need for careful manipulation of the catheters during the procedure, in order to avoid thrombo-embolic complications. In such cases, transfemoral approach may not be suitable and an alternative approach (transapical or transsubclavian) should be considered. Figure 6 summarizes the procedural approach selection algorithm. The transapical approach has the advantage of overcoming the problem of aorto–ilio-femoral vascular disease. However, it requires general anesthesia and a small anterior minithoracotomy with direct puncture of the left ventricular apex. This approach is contraindicated in patients with calcified pericardium, severe respiratory insufficiency, major chest deformity and previous left ventricular surgery using a patch [16]. In patient candidates for TAVI with MCR prosthesis who show unsuitable ilio-femoral anatomy, transsubclavian approach has been demonstrated to be feasible and safe [28,46].

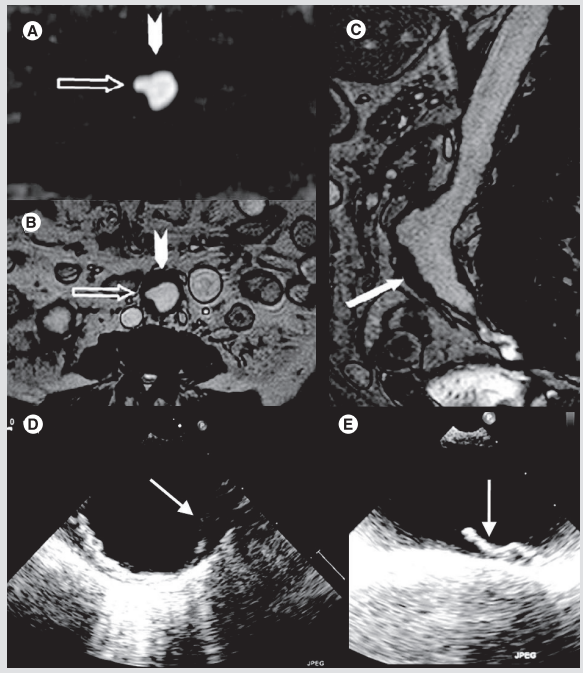

Figure 5. Evaluation of aorta with magnetic resonance angiography and transesophageal echocardiography. (A) Shows the contrast-enhanced magnetic resonance angiography image of the infrarenal aorta with suspected intramural thrombus (arrow and arrowhead). Using the true-fast imaging with steady-state precession (a hybrid T2/T1-weighted acquisition), the thrombus can be clearly differentiated from the lumen in the axial **(B)** and sagittal **(C)** images (adapted from [44], with permission from Elsevier) and presents as a contraindication to the transfemoral approach. Severe atherosclerosis of the descending aorta and the aortic arch can be detected on transesophageal echocardiography. **(D & E)** show an example of a protruding plaque in the descending aorta (arrows).

Exclusion of contraindications

Additional factors concerning the left ventricular function, coronary artery disease and presence of concomitant valvular disease (i.e., severe organic mitral valve regurgitation) must be evaluated prior to TAVI.

A detailed evaluation of left ventricular dimensions and ejection fraction should be performed in patients undergoing TAVI. Impaired left ventricular ejection fraction may increase the risk of hemodynamic instability during TAVI procedures. In addition, severe left ventricular hypertrophy with pronounced sigmoid septum at the level of the left ventricular outflow tract may prove challenging when attempting this procedure using MCR prosthesis. Moreover, the presence of left ventricular thrombus is an established contraindication for TAVI and can be better evaluated by contrast echocardiography [16].

Evaluation of coronary artery anatomy is mandatory before TAVI, as the presence of significant proximal lesions, not amenable to percutaneous coronary intervention, is considered a contraindication to TAVI [16]. Invasive coronary angiography is the gold standard for evaluation of coronary artery anatomy. By contrast, the high

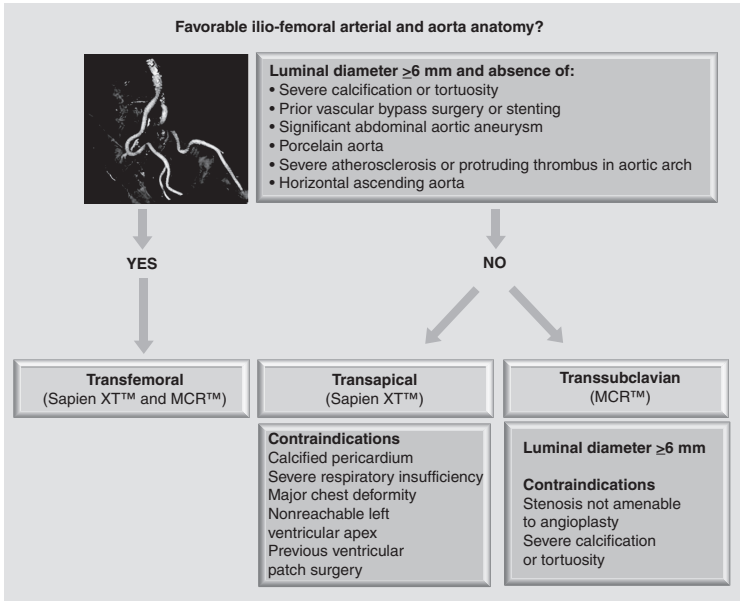

Figure 6. Transcatheter aortic valve implantation: procedural approach selection.
Data taken from [16,28,42,43].

prevalence of severe coronary artery calcification in this group of patients may challenge the assessment of coronary artery anatomy using MDCT. In patients with concomitant coronary artery stenoses, the decision of whether to perform coronary revascularization prior to TAVI has to be based on the clinical condition and the anatomy of individual patients. In a recent study of 136 patients with pre-procedural coronary angiogram who underwent TAVI, Masson and coworkers [47] reported that the early mortality and overall 1-year mortality rates did not differ between patients with no coronary artery stenoses (n = 32), patients with completely revascularized coronary lesions (n = 41) and patients with nonrevascularized or incompletely revascularized coronary lesions of varying ischemic burden (n = 63) as assessed with the Duke Myocardial Jeopardy Score [48]. Of these 136 patients, 15 patients were treated with percutaneous coronary interventions prior to TAVI (with a median time interval of 26 days between procedures; range: 3–100 days). Currently, it is generally advisable to perform revascularization in cases with severe lesions of the left main or the proximal coronary arteries before TAVI as per the current EACTS, ESC and EAPCI position statement [16].

Finally, the presence of significant organic mitral valve regurgitation increases the procedural risk. Particularly, using a MCR prosthesis, the ventricular end of the prosthesis frame may interfere with the motion of the anterior mitral leaflet resulting in or worsening mitral regurgitation [49].

Conclusion

TAVI is a feasible alternative to surgical AVR in patients with severe symptomatic AS and high operative risk. Multidisciplinary evaluation, including accurate clinical evaluation and precise assessment of aortic valve anatomy and function, aortic valve annular dimensions and peripheral artery anatomy, are crucial to optimize the results while reducing the procedural complications rate. Importantly, multimodality imaging plays an important role in the patient selection process. A summarized patient selection algorithm is detailed in Figure 7, highlighting the important factors that need to be considered before TAVI.

Future perspective

The number of TAVI procedures is increasing rapidly. Selecting the appropriate patients by detailed clinical assessment and multimodality

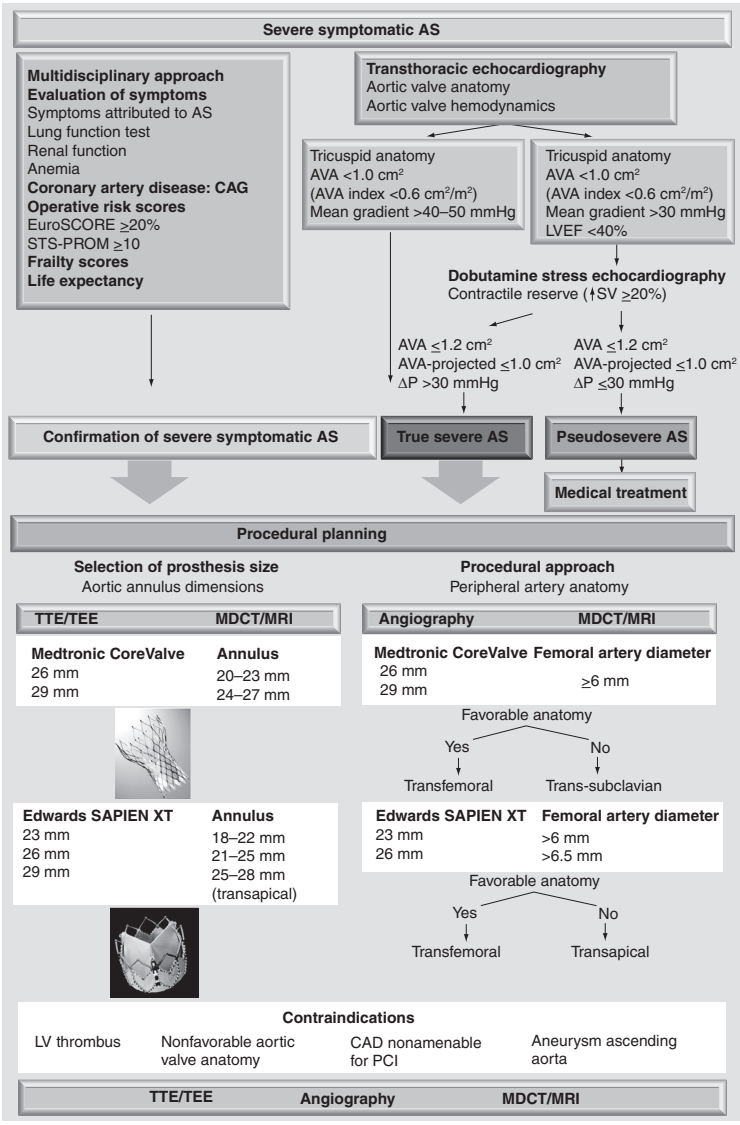

Figure 7. Summarized patient selection algorithm for transcatheter aortic valve implantation. ΔP: Increase in transvalvular gradient; AS: Aortic stenosis; AVA: Aortic valve area; CAD: Coronary artery disease; CAG: Coronary angiography; EuroSCORE: Logistic European System for Cardiac Operative Risk Evaluation; LV: Left ventricular; LVEF: Left ventricular ejection fraction; MDCT: Multidetector row computed tomography; PCI: Percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; SV: Stroke volume; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography.
Data taken from [1,2,16,25,27].

imaging techniques (the Heart team approach) can improve the results and reduce the rate of complications to a minimum. However, a number of questions still need to be answered. In particular, the reference method and imaging modality to size the aortic valve annulus (TTE/TEE/MDCT/MRI) needs to be defined. In addition, vascular complications and a high rate of atrioventricular conduction block (and the need for a pacemaker, especially with MCR prosthesis) are the main safety issues that remain to be improved. Ongoing research aims to improve the current technology and provide lower profile delivery systems that may help to reduce the number of vascular complications. In the coming years, data on prosthesis durability are eagerly awaited. Degeneration and dysfunction of current transcatheter prosthesis is currently uncommon [10,50]. A transcatheter prosthesis, with durability comparable to that of conventional surgical bioprosthesis, would probably allow this technique to be expanded to younger patients in the future. While awaiting further developments in this technology, patient selection, according to the current recommendation, should be adhered to stringently to increase the success rate of the procedures and minimize the procedural-related complications.

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Executive summary

Survival after transcatheter aortic valve implantation in patients with symptomatic aortic stenosis who are not suitable for surgical aortic valve replacement

- The PARTNER trial demonstrated that transcatheter aortic valve implantation (TAVI) was associated with better survival at 1-year, compared with standard therapy.
- Requires longer follow-up study to provide data on long-term prosthesis durability and outcomes of patients who underwent TAVI.

Clinical risk assessment before TAVI

- A multidisciplinary team approach is essential when making accurate and unbiased clinical assessment.
- TAVI is currently restricted to patients with very high operative risk for surgery and a life expectancy of ≥1year.
- High operative risk patients are those with a logistic European System for Cardiac Operative Risk Evaluation (EuroScore) >20% and Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM score) >10%.

Confirmation of aortic stenosis severity

- Severe aortic stenosis (AS) is primarily assessed by echocardiography and is defined as an aortic jet velocity >4m/s and/or a mean pressure gradient >40–50 mmHg and/or an aortic valve area <1 cm^2 (or 0.6 cm^2/m^2 indexed to body surface area).
- Dobutamine stress echocardiography should be performed in patients with low flow, low gradient AS to distinguish between true severe AS from pseudosevere AS.

There are two currently available transcatheter prostheses

- The prostheses are balloon expandable Sapien XT™ (size 23 and 26 mm for aortic valve annulus 18–21 and 22–25 mm, respectively) and self-expandable Medtronic CoreValve Revalving system™ (size 26 and 29 mm for aortic valve annulus 20–23 and 23–27 mm, respectively).
- Retrograde transarterial (transfemoral or transsubclavian) or antegrade transapical are the procedural approaches.

Evaluation of TAVI feasibility & procedural planning

- Multimodality imaging is essential to optimize procedural success and to avoid complications.
- Aortic valve annular dimensions will determine the prosthesis size, whereas peripheral artery anatomy will determine the procedural approach.
- Exclusion of contraindications: bicuspid aortic valve, severe proximal coronary artery stenosis not amenable to percutaneous intervention and presence of left ventricular thrombus are established contraindications for TAVI.

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Imaging and quantification of aortic regurgitation after TAVI

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Imaging and quantification of aortic regurgitation after TAVI

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KEYWORDS

- aortic regurgitation
- transcatheter aortic valve implantation
- cardiac imaging

Abstract

During the last decade, transcatheter aortic valve implantation (TAVI) techniques have evolved rapidly providing several systems that conform to a broad spectrum of aortic valve annulus sizes, developing new delivery systems that provide an alternative to patients with difficult vascular access and permitting more controlled and accurate prosthesis deployment that result in improved procedural outcomes. However, residual aortic regurgitation (AR) (paravalvular or transvalvular) remains a recurrent observation and patients with moderate or severe AR have a reduced mid-term prognosis Therefore, postprocedural AR should be carefully and accurately evaluated in order to decide whether additional procedures such as re-ballooning or valve-in-valve are needed to reduce AR severity, and changes in AR at follow-up should be monitored. In the current review, the role of cardiac imaging to understand the mechanism underlying AR after TAVI and to quantify the severity of AR will be discussed.

Introduction

Transcatheter aortic valve implantation (TAVI) is now an accepted standard of care for patients with symptomatic severe aortic stenosis (AS) who are not candidates for surgery or have high surgical risk. Over the past decade, the combined effect of learning curve, improvement in transcatheter device technology, a better understanding of aortic root anatomy, together with careful patient selection have gradually resulted in an improved clinical outcome for patients undergoing TAVI[1]. However, aortic regurgitation (AR) remains a common phenomenon following TAVI. Experience in large multicentre studies and registries, including over 6,000 patients, revealed that the incidence of AR after TAVI ranged from 48 to 93% of patients, with comparable prevalence between self- and balloon-expandable prostheses **(Table 1)**[2-10]. Trace or mild paravalvular AR is a common finding in the majority of patients, whereas only 14-21% of patients may have at least moderate AR following TAVI **(Table 1)**[2-10]. The observed variation in AR after TAVI may be related to the use of different modalities to assess AR (angiography, transoesophageal [TEE] or transthoracic [TTE] echocardiography), the different timing of AR assessment after TAVI (immediately post deployment, before hospital discharge and at 30-day follow-up) and the lack of a standardised protocol to grade AR severity (qualitative versus semi-quantitative methods). Accurate assessment of AR after TAVI is clinically relevant since moderate and severe post-procedural AR have been associated with poor treatment response[11], early in-hospital death[2] and mid-term mortality[3,5,8,11]. In addition, a recent report has suggested that residual AR grade >1 may also be associated with reduced survival[12]. Conversely, serial evaluations have shown that the severity of AR tends to reduce over time[3,13,14]. Current recommendations to characterise and quantify the severity of AR post TAVI include the morphology and location of the regurgitant jet, as well as the percentage of the circumference of the prosthesis occupied by the regurgitant jet. The value of cardiac imaging to evaluate the mechanisms underlying AR after TAVI and to quantify its severity will be discussed in this review.

Mechanisms of AR after TAVI

AR following TAVI can be categorised according to the location of the AR jet in relation to the prosthesis: either paravalvular AR (PAR) (between the prosthesis and the native annulus), transvalvular AR (TAR) (within the prosthesis) or both, and is best appreciated using colour-flow Doppler echocardiography **(Figure 1)**.

PAR can be due to incomplete annular sealing of the transcatheter valve. With conventional aortic valve surgery the native aortic valve is removed and the prosthesis is sewn onto the decalcified annulus, but in TAVI the native calcified aortic leaflets are displaced to accommodate the newly implanted prosthesis. The

Table 1. Prevalence of postprocedural aortic regurgitation after transcatheter aortic valve implantation.

	Canadian registry[6]	SOURCE registry[39]	PARTNER B[4]	PARTNER A[7]	Unbehaun et al[10]	Tamburino et al[8]	UK-TAVI registry[5]	German-TAVI registry[2]	FRANCE 2 registry[3]
Time of recruitment, yr	Jan 2005 - Jun 2009	Nov 2007 - Jan 2009	May 2007 - Mar 2009	May 2007 - Aug 2009	Apr 2008 - Mar 2011	Jun 2007 - Dec 2009	Jan 2007 - Dec 2009	Jan 2009 - Dec 2009	Jan 2010 - Oct 2011
Patients, n	339	1,038	179	348	358	663	870	697	3,195
Edwards, %	100	100	100	100	100	–	47	15.6	67
CoreValve, %	–	–	–	–	–	100	52	84.4	33
Transfemoral, %	49	45	100	70	–	90	69	92	75
Non-transfemoral, %	51	55	–	30	100	10	31	8	25
AR assessment	TTE	TTE	TTE	TTE	Angio/TEE	TTE	Angio	Angio	TTE
Postprocedural any AR									
None, %	16	–	6	11	52	–	39	28	
Trace/mild, %	78	–	78	76	47	–	47	55	
Mod/severe, %	6	1.9	15	13	1	21	14	17	
Postprocedural PAR									
None, %	–	–	14	23	–	–	–	–	38
Trace/mild, %	–	–	68	65	–	–	–	–	46
Mod/severe, %	–	–	12	12	–	21	14	–	16
Postprocedural TAR									
None, %		–	31	35	–	–	–	–	91
Trace/mild, %		–	67	64	–	–	–	–	8
Mod/severe, %		–	1	1	–	–	–	–	1

Angio: angiography; PAR: paravalvular aortic regurgitation; TAR: transvalvular aortic regurgitation; TEE: transoesophageal echocardiography; TTE: transthoracic echocardiography; yr: year
*Included only AR >grade 2 (severe AR).

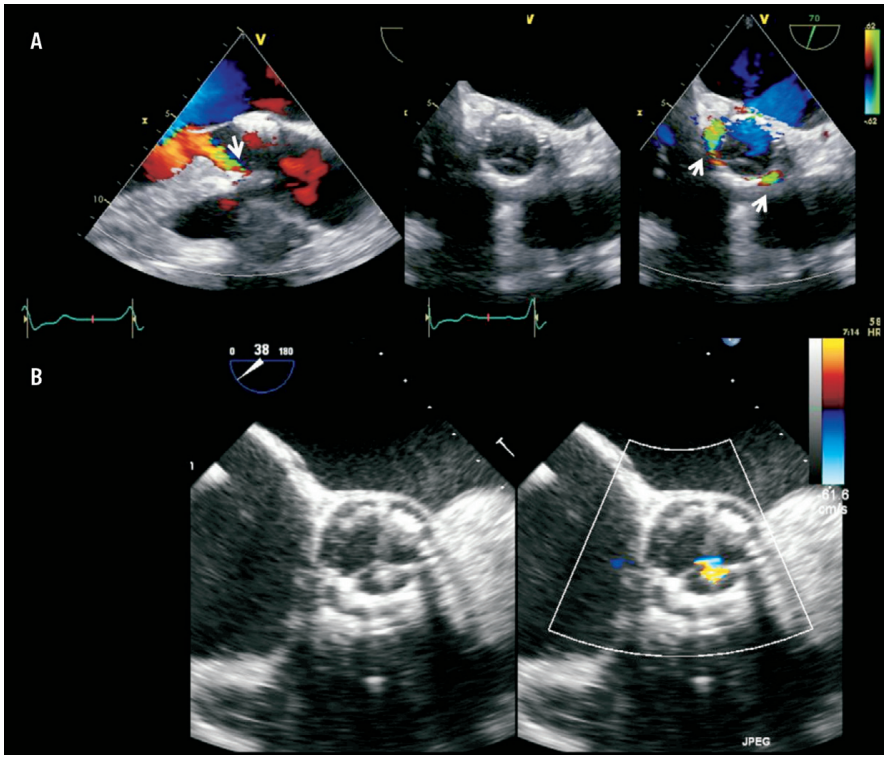

Figure 1. *Panel A shows the long-axis view of the aortic root on conventional 2-D transoesophageal echocardiography of a patient who underwent transcatheter aortic valve implantation with a balloon-expandable valve. The arrow indicates the presence of mild paravalvular regurgitation at the level of the anterior part of the aortic annulus. The short-axis views show the exact location of the two jets of paravalvular regurgitation (arrows). Panel B shows a patient with transvalvular regurgitation, best noted on the short-axis view on transoesophageal echocardiography.*

presence of asymmetrical/bulky aortic valve calcification has been related to the presence of PAR **(Figure 2)**[10,15-18]. Exact localisation of calcium in the aortic root and valve may predict PAR after TAVI[19,20]. Particularly, calcification of the commissures has been associated with PAR but calcification of the body or the edge of the aortic cusps did not increase the risk of PAR[20,21]. Other phenomena related to PAR include prosthesis undersizing[18,22,23], bicuspid valve (asymmetrical expansion)[24], incorrect depth of implantation (too high or low implantation without apposition to annular tissue) and an increased angle of the left ventricular outflow tract (LVOT) to the ascending aorta[25]. Multidetector row computed tomography is a valuable preprocedural imaging technique providing accurate sizing of the aortic annulus, precise characterisation of aortic valve anatomy and aortic root dimensions, and localisation of calcifications in the landing zone **(Figure 2)**[20,22,23].

In contrast, TAR is less often observed and may arise from valvular obstruction (from stiff guidewire or pigtail catheter or an overhanging native leaflet resulting in improper leaflet closure)[26,27], valvular damage (during crimping process or overexpansion following post-dilatation)[26,28] or prosthesis oversizing (suboptimal stent expansion or impaired leaflet mobility). Prompt recognition of TAR and its mechanism is crucial, so that appropriate interventions such as manipulation of catheter or implantation of a second prosthesis (valve-in-valve procedure) can be performed in a timely manner to ensure good clinical outcome.

Imaging and quantification AR after TAVI

Currently, AR after TAVI is largely assessed using angiography, echocardiography or both. Using supra-aortic angiography, the degree of postprocedural AR is determined qualitatively by visual

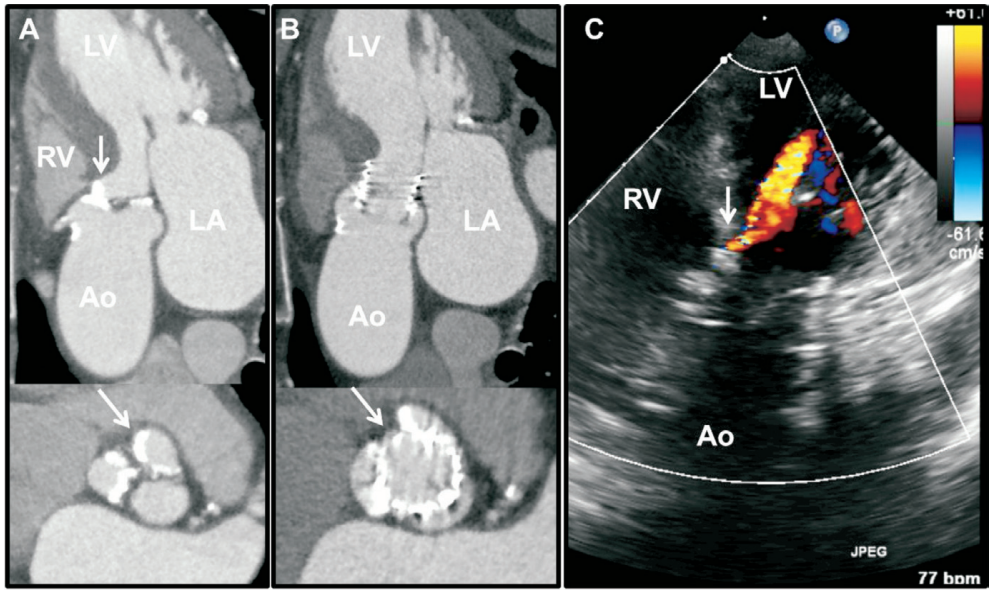

Figure 2. *Panel A shows a calcified tricuspid aortic valve of a patient with bulky calcification mainly in the non-coronary (arrow) and right cusps, and extending to the base of the interventricular septum (arrow) on multidetector computed tomography (MDCT). Following TAVI with a balloon-expandable (SAPIEN XT) valve, a paravalvular leak was observed with colour-coded Doppler transoesophageal echocardiography (TEE) that coincided with the location of the bulky calcification at the commissure between the right and non-coronary cusps on MDCT. Panel B shows the deployed frame and the arrow indicates the gap at the level of the commissure between the non-coronary and right cusps. Panel C shows the colour-coded Doppler TEE in a transgastric view with the paravalvular leak in the location of the calcification at right to non-coronary commissure.*

estimation of the concentration of contrast medium (regurgitation volume) in the left ventricle (LV) and classified into four grades: absent (grade 0), trace or mild (grade 1), mild-to-moderate (grade 2), moderate-to-severe (grade 3) and severe (grade 4)[29]. Although this is a commonly used method of assessment during TAVI, it lacks accurate quantification and has limited sensitivity in differentiating PAR from TAR **(Figure 3)**. Moreover, this modality is not preferred for serial AR evaluation after TAVI.

The other widely used method for AR assessment is echocardiography, and TEE is frequently performed to help guide transcatheter valve deployment and to detect complications during TAVI[30]. In addition, it permits assessment of the position and function of the prosthesis, including determination of the presence/severity and mechanism of AR immediately after valve deployment. In the setting of TAVI, it is critical to distinguish PAR from TAR and to determine its severity rapidly so as to allow for manoeuvres such as re-ballooning, attempting maximal expansion of the prosthesis in the presence of significant PAR or deployment of a second valve in the presence of severe TAR. Using the standard long- and short-axis views of colour Doppler TEE, PAR and TAR can both be accurately detected. With the current three-dimensional matrix array TEE probes, simultaneous display of two orthogonal real-time images (biplane long- and short-axis views) with superimposed colour flow Doppler imaging allows further delineation and exact localisation of the PAR **(Figure 4)**. However, accurate quantification of PAR remains challenging as it frequently consists of multiple small jets, origins of which may be obscured by the prosthesis stent/frame. Current recommendations for AR assessment after TAVI are derived from native valvular regurgitation, using multi-parametric approaches **(Table 2)**[31,32]. In the setting of TAVI, modifications are required as the grading for PAR differs from that of TAR, with emphasis on the "jet anatomy" classification. For example, the width of the proximal AR jet relative to the LVOT diameter is the suggested criterion for semi-quantitative assessment of TAR severity **(Figure 5)**. In contrast, as PAR is frequently eccentric and irregular in shape, the proportion of the circumference of the prosthesis covered by the AR jet provides semi-quantitative assessment of PAR severity. However, this approach does not take into considera-

Table 2. Recommended criteria for aortic regurgitation (paravalvular and transvalvular) after transcatheter aortic valve implantation.

Parameter	Mild	Moderate	Severe
Valve structure and motion	Usually normal	Usually abnormal	Usually abnormal
Left ventricular size	Normal	Normal/mildly dilated	Dilated
Doppler parameters (qualitative or semi-quantitative)			
Jet width in central jets (%LVOT): colour[a]	≤25%	26-64%	≥65%
Jet density: continuous-wave	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): continuous-wave[b]	Slow (>500 ms)	Variable (200-500 ms)	Steep (<200 ms)
LVOT versus pulmonary flow: pulsed-wave	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in descending aorta: pulsed-wave	Absent or brief early diastolic	Intermediate	Prominent/holodiastolic
Circumferential extent of paravalvular leak (%): colour[c]	10-20	10-20	>20
Doppler parameters (quantitative)			
Regurgitant volume (mL)	<30	30-59	>60
Regurgitant fraction (%)	<30	30-50	>50

LVOT: left ventricular outflow tract; PHT: pressure half time; [a]parameter applicable to central jets (less accurate in eccentric jets); [b]parameter influenced by left ventricular compliance; [c]for paravalvular aortic regurgitation

tion the presence of multiple jets (unknown validity of summation of all the jets) and the possible contamination from the radial extent of PAR jets, which may result in overestimation of the AR severity[32]. Finally, with the currently available 3-D colour full volume echocardiographic data sets, direct planimetry of the AR vena contracta may provide an accurate quantitative assessment of AR severity **(Figure 5)**. Recently, Goncalves and co-workers showed that quantitative assessment of PAR after TAVI was feasible by planimetry of the vena contracta obtained with 3-D TTE[33]. The 3-D approach provided a better correlation between the AR volume and the vena contracta as compared to 2-D TTE.

Localisation of the PAR based on the standard parasternal short-axis TTE view of the aortic prosthesis is possible. In addition to a direct measurement of the vena contracta[33], 3-D TTE may provide a more accurate calculation of the total stroke volume (both the regurgitant and forward stroke volumes) by subtracting LV end-systolic from LV end-diastolic volumes[34]. In the absence of significant mitral regurgitation, this method may be highly accurate since it is independent of geometric assumptions and is not hampered by foreshortened views. Therefore, 3-D echocardiography may become the method of choice for assessing complicated AR such as that following TAVI, although it requires further validation before widespread implementation in clinical routine.

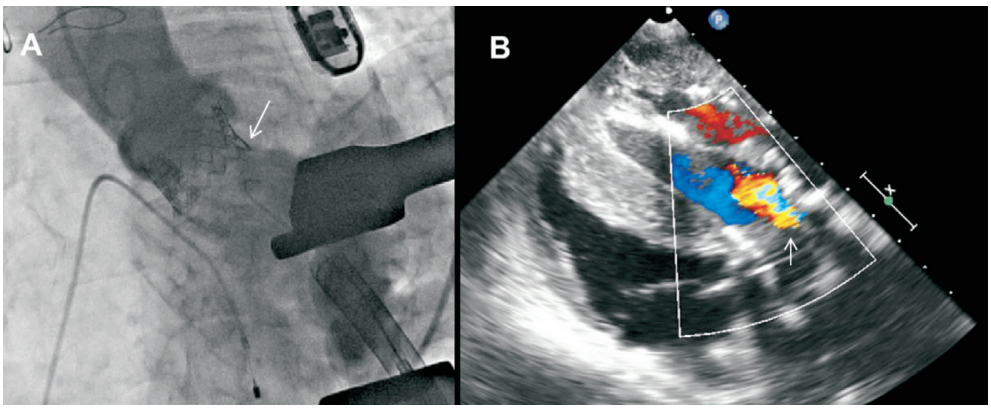

Figure 3. *Assessment of aortic regurgitation (AR) after TAVI. Panel A shows supra-aortic angiography to estimate the AR grade. In contrast to echocardiography, angiography has limited resolution to differentiate between paravalvular and transvalvular AR. Panel B shows the TEE 120° transgastric view of the same patient. The arrow indicates the presence of a wide regurgitant jet in the valve due to a frozen cusp.*

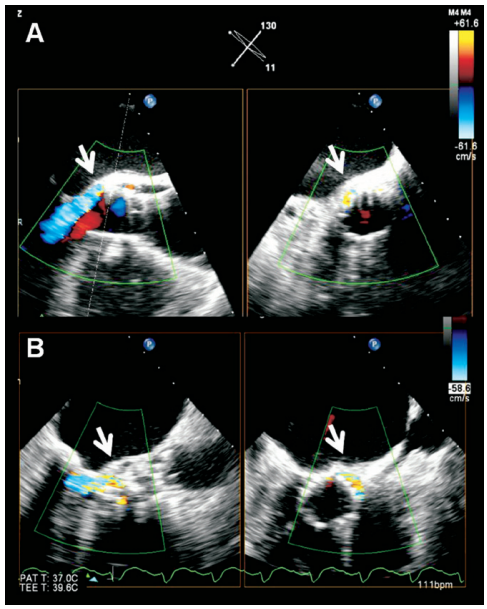

Figure 4. *Current 3-D transoesophageal probes permit simultaneous visualisation of the transcatheter aortic valve in orthogonal (long- and short-axis) views to exactly localise the paravalvular leak. The arrows indicate that the paravalvular leak is located at the posterior part of the aortic annulus, close to the anterior mitral valve leaflet. The paravalvular leak is mild in severity as it occupies <10% of the circumference of the prosthetic valve (A) and is moderate in severity as it occupies 10-20% of the circumference of the prosthetic valve (B).*

The feasibility of magnetic resonance imaging (MRI) for quantification of AR post TAVI has been evaluated: particularly velocity-encoded phase imaging permits measurement of blood flow velocity and volume across the valve and calculation of the regurgitant fraction (ratio of forward to backflow volume across the valve). A recent study including 16 patients who underwent MRI following TAVI demonstrated a significant correlation between MRI-derived and angiography-estimated degree of AR ($r=0.86$, $p<0.001$) while only a limited correlation between MRI and 2-D TTE was observed ($r=0.32$, $p=0.23$)[35]. Moreover, TTE underestimated AR by at least one grade when compared to MRI in 44% of patients, indicating the limitations of 2-D imaging for assessment of eccentric AR, in particular PAR post-TAVI[35].

Experience of AR assessment after TAVI and when to measure

Acute postprocedural evaluation of AR after TAVI is crucial since the presence of moderate and severe AR is associated with increased mortality at follow-up and several manoeuvres can be performed at the catheterisation laboratory/hybrid operating theatre to reduce the severity of AR. In addition, the presence of AR should be monitored during the days after TAVI since the regurgitation grade may change **(Table 3)**. For example, the properties of the self-expandable prosthesis may lead to a reduction in the grade of PAR at follow-up. In 126 patients undergoing TAVI with self-expandable prostheses, Buellesfeld et al reported a reduction in the prevalence of PAR of any grade from 41% at 30 days after TAVI to 37% at two-year follow-up[13]. Experience with the balloon-expandable prostheses has also shown a progressive reduction in the prevalence of AR after TAVI. In the PARTNER cohort A trial, AR improved in 31.5% of patients at two-year follow-up[14]. Conversely, in the FRANCE 2 registry with 3,195 patients, the prevalence of AR remained unchanged at one-year follow-up[3].

Anatomo-pathological analyses of explanted self-expandable prostheses have demonstrated neointimal coverage of the frame struts in contact with the aortic wall but not in areas of high velocity blood flow such as the coronary ostia[36]. This neointimal tissue may be beneficial in reducing the grade of PAR by closing the gaps between the prosthetic frame and the native annulus. However, it has been suggested that, in specific circumstances, this tissue proliferation may lead to more rapid structural valve deterioration. So far, structural valve deterioration is anecdotal[37,38] and other complications such as stent fracture, deformation or valve migration have not been described.

Table 3. Progression of aortic regurgitation after transcatheter aortic valve implantation.

	Patients, n	CoreLab	Prosthesis	AR,% (none / trace-mild / moderate-severe)			
				Postprocedure	1-year	2-year	3-year
REVIVAL[40]	84	Yes	Edwards 100%	20 / 37 / 23	9 / 22 / 18	4 / 6 / 12	2 / 4 / 8
PARTNER B[41]	179	Yes	Edwards 100%	6 / 78 / 15	11 / 71 / 15	34 / 61 / 5	–
PARTNER A[14]	348	Yes	Edwards 100%	11 / 76 / 13	13 / 80 / 7	32 / 6 / 7	–
Buellesfeld et al[13]	126	No	CoreValve 100%	59 / 32 / 9	63 / 34 / 3	63 / 37 / 0	–
Ussia et al[42]	181	No	CoreValve 100%	32 / 53 / 15	34/ 48 / 18	–	43 / 47 / 10
Gilard et al[3]	3,195	No	Edwards 67% CoreValve 33%	38 / 46 / 16	33 / 47 / 20	–	–

AR: aortic regurgitation

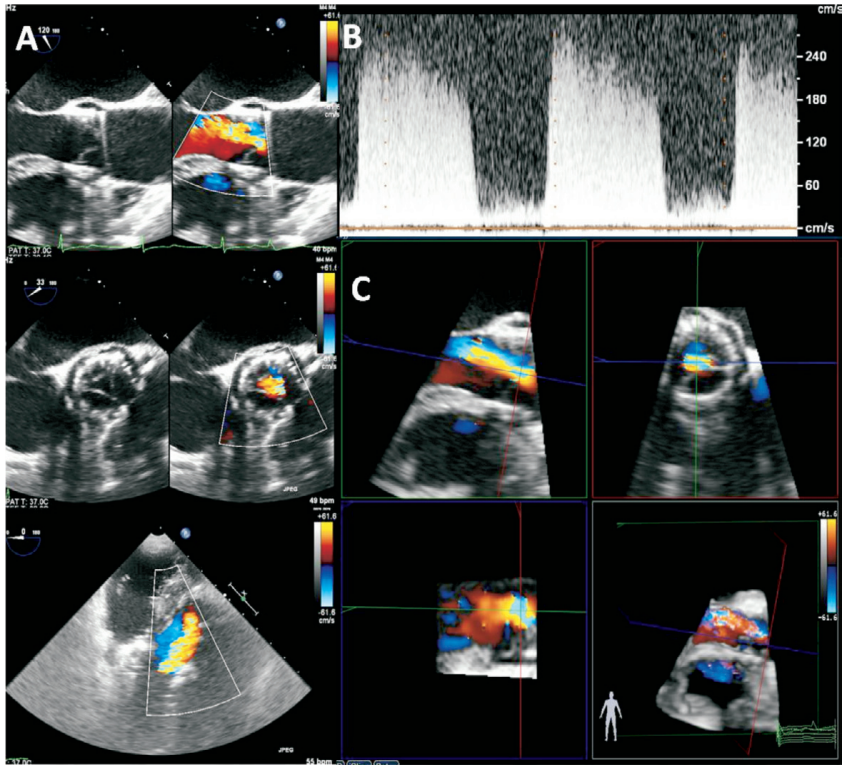

Figure 5. *An example of moderate-to-severe transvalvular aortic regurgitation (AR) after TAVI, assessed semi-quantitatively using Doppler parameters: a jet width that occupied 45% of the LVOT diameter (A), a dense CW Doppler signal and a steep jet deceleration rate (B). 3-dimensional colour-coded Doppler permits quantitative evaluation of AR using multiplanar reconstruction by planimetry of the regurgitant vena contracta area (C), which is performed by selecting the best frame to visualise the AR jet. The 3-D dataset was manually cropped to provide a cross-sectional plane through the vena contracta of the AR jet, perpendicular to the direction of the jet. From the en face view of the vena contracta and selecting the plane with the narrowest cross-sectional area of the regurgitant jet, planimetry of the vena contracta can be performed.*

Conclusions

AR after TAVI has been associated with worse outcome and increased mortality at follow-up. Accurate assessment of AR during the procedure is crucial to decide whether additional manoeuvres such as re-ballooning or valve-in-valve are needed to reduce the AR grade. Supra-aortic angiography or echocardiography (particularly 3-D TEE) are the preferred imaging techniques to assess AR immediately after valve deployment. In addition, continued evaluation of AR at follow-up is recommended since the grade of AR may change over time. For follow-up assessment, transthoracic echocardiography, particularly 3-D TTE, is the preferred imaging technique.

Conflict of interest statement

V. Delgado received consulting fees from Medtronic and St. Jude Medical. The Department of Cardiology received research grants from Lantheus Medical Imaging, Boston Scientific, Sadra Lotus, Medtronic, St. Jude Medical, Biotronik, Edwards Lifesciences and GE Healthcare. The other authors have no conflicts of interest to declare.

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Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation

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Location and Severity of Aortic Valve Calcium and Implications for Aortic Regurgitation After Transcatheter Aortic Valve Implantation

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Location of aortic valve calcium (AVC) can be better visualized on contrast-enhanced multidetector row computed tomography. The present evaluation examined whether AVC severity and its location could influence paravalvular aortic regurgitation (AR) after transcatheter aortic valve implantation. A total of 79 patients (age 80 ± 7 years, 49% men) with preprocedural multidetector row computed tomography were included. Volumetric AVC quantification and its location were assessed. Transesophageal echocardiography was performed to assess the presence and site of AR after transcatheter aortic valve implantation. Receiver operating characteristic curves were generated to evaluate the usefulness of AVC in determining paravalvular AR at a specific site. Postprocedural AR of grade 1 or more was observed in 63 patients. In most patients (n = 56, 71%), AR was of paravalvular origin. Calcium at the aortic wall of each valve cusp had the largest area under the curve (0.93, p <0.001) in predicting paravalvular AR at the aortic wall site compared to calcium at the valvular edge or body (area under the curve 0.58 and 0.67, respectively). Calcium at the valvular commissure was better than calcium at the valvular edge (area under the curve 0.94 vs 0.71) in predicting paravavular AR originating from the corresponding commissure. In conclusion, contrast-enhanced multidetector row computed tomography can be performed to quantify AVC. Both AVC severity and its exact location are important in determining paravalvular AR after transcatheter aortic valve implantation. **© 2011 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2011;108:1470–1477)**

Multidetector row computed tomography (MDCT) allows visualization of the precise location of aortic valve calcium (AVC).[1,2] The present evaluation aimed to determine whether the severity and location of AVC would influence the occurrence and location of paravalvular aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI).

Methods

A total of 79 patients with symptomatic, severe aortic stenosis (AS) who underwent MDCT before TAVI were included. The patients with bicuspid aortic valves or failing bioprosthetic valves (valve-in-valve) and those who did not eventually receive TAVI were excluded. An Edwards-Sapien device (Edwards Lifesciences, Irvine, California) was implanted in all patients using either the transfemoral or transapical approach.

According to the institutional protocol, all patients underwent a detailed clinical evaluation and preoperative transthoracic echocardiography to examine AS severity, valve morphology, and left ventricular (LV) function. Preoperative multidetector row computed tomographic scans were also performed to assess the aortic valve and aortic root and the extent and distribution of AVC.[3] Transesophageal echocardiography (TEE) was performed intraprocedurally and to evaluate the function of the prosthesis immediately after valve deployment, including the assessment of the AR location, if present.[3] The clinical, echocardiographic, and multidetector row computed tomographic data were prospectively collected in an electronic patient dossier (EPD Vision, version 8.3.3.6, Leiden, The Netherlands) and retrospectively analyzed.

The patients underwent imaging preoperatively using a commercially available ultrasound system (Vingmed Vivid-7, General Electric Vingmed, Horten, Norway). A complete 2-dimensional, color, pulsed, and continuous-wave Doppler echocardiographic examination was performed.[3–5] The LV end-diastolic volume and end-systolic volume were measured (indexed to the body surface area), and the LV ejection fraction was derived using biplane Simpson's method.[3,4] Aortic valve morphology

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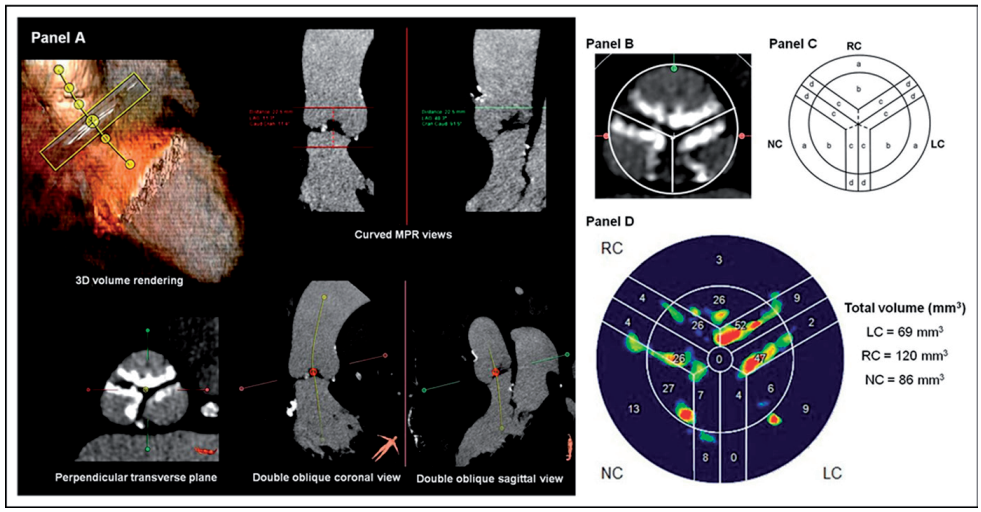

Figure 1. *(A)* Automatic segmentation of aortic root with center line by dedicated software (3mensio Valve, version 4.1.sp2, 3mensio Medical Imaging BV). By moving the 2 orthogonal MPR planes and the third perpendicular transverse plane, manual adjustment of the center line is possible. Next, by moving the transverse plane along the center line, the region of interest for quantification of calcium is defined manually using the help of the curved MPR view (from the level of the LV outflow tract proximally to the level just below the coronary ostia distally). From the transverse MPR view *(B)*, the aortic valve is automatically divided into 3 cusps and manual adjustment of the divisions (arms) between the cusps is possible. The software will automatically detect areas of calcium according to the predetermined threshold set by the user and provide their locations and corresponding volumetric measurements *(C, D)*. *(D)* Example shown. *(C)* Six locations of calcium can be identified on each cusp. a = along aortic wall; b = valvular body; c = valvular edge; d = commissure; LC = left coronary cusp; NC = noncoronary cusp; RC = right coronary cusp.

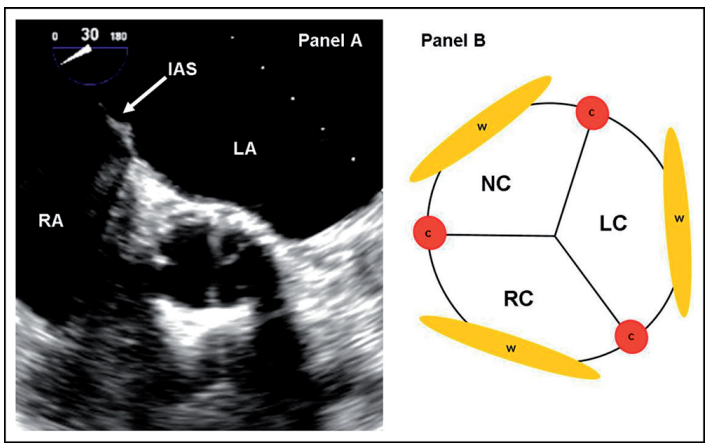

Figure 2. Identification of sites of AR after TAVI using TEE. Short-axis view, at level of proximal (ventricular) end of prosthesis, permits visualization of origin of paravalvular regurgitation. Interatrial septum helps to identify the noncoronary cusp *(A)*. *(B)* Six possible sites of paravalvular regurgitation. c = commissure site; IAS = interatrial septum; LA = left atrium; LC = left coronary cusp; NC = noncoronary cusp; RA = right atrium; RC = right coronary cusp; w = aortic wall site.

was evaluated using the parasternal short-axis view, and the valve area was determined by the continuity equation.[6] The peak and mean transaortic pressure gradients were calculated.[6] AR was assessed using color Doppler after optimizing the gain and Nyquist limit, and its severity was assessed.[7]

Table 1
Baseline clinical characteristics before transcatheter aortic valve implantation (TAVI)

Variable	All (n = 79)	Paravalvular AR (n = 56)	No Paravalvular AR (n = 23)	p Value
Men	39 (49%)	30 (54%)	9 (39%)	0.32
Age (years)	80 ± 7	80 ± 7	81 ± 6	0.54
Body mass index (kg/m^2)	25.5 ± 4.6	24.9 ± 3.0	26.8 ± 7.0	0.22
Body surface area (m^2)	1.82 ± 0.19	1.84 ± 0.17	1.78 ± 0.22	0.18
Logistic EuroSCORE (%)	23 ± 13	23 ± 12	21 ± 14	0.44
Hypertension	46 (58%)	32 (57%)	14 (61%)	0.81
Hypercholesterolemia	33 (42%)	21 (38%)	12 (52%)	0.32
Diabetes mellitus	22 (28%)	18 (32%)	4 (17%)	0.27
Peripheral vascular disease	23 (29%)	16 (29%)	7 (30%)	1.00
Previous myocardial infarction	19 (24%)	13 (23%)	6 (26%)	0.78
Previous coronary artery bypass	31 (39%)	24 (43%)	7 (30%)	0.45

Continuous data are presented as mean ± SD and categorical data as n (%).
EuroSCORE = European System for Cardiac Operative Risk Evaluation.

Table 2
Baseline echocardiographic characteristics before transcatheter aortic valve implantation (TAVI)

Variable	All (n = 79)	Paravalvular AR (n = 56)	No Paravalvular AR (n = 23)	p Value
Left ventricular end-diastolic volume (ml/m^2)	67 ± 26	70 ± 27	58 ± 21	0.06
Left ventricular end-systolic volume (ml/m^2)	35 ± 23	37 ± 24	30 ± 22	0.18
Left ventricular ejection fraction (%)	52 ± 12	51 ± 14	54 ± 15	0.39
Mean transaortic gradient (mm Hg)	40 ± 14	38 ± 16	38 ± 12	0.94
Peak transaortic gradient (mm Hg)	61 ± 22	62 ± 24	60 ± 17	0.79
Aortic valve area (cm^2)	0.74 ± 0.18	0.76 ± 0.18	0.69 ± 0.18	0.15
Aortic regurgitation				
None	18 (23%)	11 (20%)	7 (30%)	0.61
Mild	48 (61%)	35 (63%)	13 (57%)	
Moderate	13 (16%)	10 (17%)	3 (13%)	
Severe	0	0	0	

Continuous data are presented as mean ± SD and categorical data as n (%).

All patients underwent preoperative evaluation of the aortic valve and aortic root with either a 64-detector or 320-detector row computed tomography scanner (Aquilion 64 and Aquilion ONE, respectively, Toshiba Medical Systems, Otawara, Japan). The acquisition protocols of the multidetector row computed tomographic data for the Aquilion 64 and Aquilion ONE have been previously described.[8] Before each scan, the patients with a heart rate greater than the threshold of 65 beats/min received oral β blockers (50 to 100 mg metoprolol), unless contraindicated. All multidetector row computed tomographic scans were acquired during midinspiratory breath-hold. To synchronize the arrival of the contrast media, bolus arrival was detected using a real-time bolus tracking technique with a threshold of +180 Hounsfield units. All the multidetector row computed tomographic data sets were recorded and stored for postprocessing.

The assessment of AVC was performed using the diastolic images, at 75% of the RR interval of the contrast-enhanced multidetector row computed tomographic scans.[8] The region of interest on the aortic valve, from which AVC quantification was performed, included (from proximal to distal) the LV outflow tract, aortic annulus, valvular cusps, and the adjacent aortic walls (until the level before the appearance of coronary ostium distally on the double oblique transverse view). Mitral annular calcification and atherosclerosis of the upper aortic root (distal to the coronary ostia level) were excluded from AVC quantification. AVC was measured quantitatively using a novel automated data postprocessing software (3mensio Valve, version 4.1.sp2, 3mensio Medical Imaging BV, Bilthoven, The Netherlands). An empiric threshold of ≥800 Hounsfield units was used to detect areas of calcium in the region of interest, because the luminal contrast enhancement ranged from 250 to 760 Hounsfield units. As previously reported,[9,10] calcium quantification using the Agatston score requires a nonlinear weighting factor in its derivation and thus has been shown to exhibit greater variability than the volumetric quantification of calcium. Accordingly, we quantified AVC in cubic millimeters instead of using the Agatston score.

First, from the 3 multiplanar reformation (MPR) planes and the 3-dimensional reconstruction, the aortic root was automatically segmented and a center line crossing the aortic lumen displayed (Figure 1). The center line and the perpendicular MPR plane were manually adjusted to improve accuracy using the aortic cusps as a guide, whereby the 2 orthogonal MPR planes would bisect the long axis of the aortic cusps in parallel, and a third perpendicular transverse plane would bisect the 3 aortic cusps. The true trans-

Table 3
Baseline multidetector row computed tomographic measurements of total volume of aortic valve calcium (AVC) and its respective location at aortic cusp in patients with and without paravalvular aortic regurgitation (AR)

Variable	Paravalvular AR (n = 56)	No Paravalvular AR (n = 23)	p Value
Total calcium volume (mm^3)	367.1 ± 35.9	222.3 ± 43.3	0.023*
Calcium on left cusp (mm^3)	105.4 ± 14.3	40.6 ± 10.5	0.007*
Calcium on right cusp (mm^3)	102.2 ± 13.1	61.9 ± 77.3	0.082
Calcium on noncoronary cusp (mm^3)	160.2 ± 16.6	95.9 ± 19.3	0.028*
Calcium on wall of left cusp (mm^3)	28.6 ± 3.5	10.8 ± 5.4	0.008*
Calcium on wall of right cusp (mm^3)	25.0 ± 4.7	11.5 ± 7.1	0.12
Calcium on wall of noncoronary cusp (mm^3)	46.1 ± 6.1	19.0 ± 11.9	0.029*
Calcium on edge of left cusp (mm^3)	33.3 ± 5.9	15.6 ± 5.6	0.076
Calcium on edge of right cusp (mm^3)	37.7 ± 5.7	25.6 ± 5.8	0.21
Calcium on edge of noncoronary cusp (mm^3)	42.7 ± 7.0	33.0 ± 7.5	0.42
Calcium on body of left cusp (mm^3)	29.2 ± 6.1	10.6 ± 2.9	0.060
Calcium on body of right cusp (mm^3)	23.8 ± 5.0	13.2 ± 4.5	0.20
Calcium on body of noncoronary cusp (mm^3)	54.7 ± 7.3	34.8 ± 7.8	0.11
Calcium on left–right commissure (mm^3)	13.4 ± 2.2	2.8 ± 1.1	0.003*
Calcium on left–noncoronary commissure (mm^3)	9.8 ± 2.7	1.2 ± 0.6	0.050
Calcium on right–noncoronary commissure (mm^3)	12.5 ± 2.5	6.1 ± 1.8	0.11
Calcium on left–right edge (mm^3)	36.1 ± 6.6	20.0 ± 5.9	0.15
Calcium on left–noncoronary edge (mm^3)	40.5 ± 6.4	23.3 ± 4.0	0.098
Calcium on right–noncoronary edge (mm^3)	37.2 ± 5.7	30.8 ± 8.4	0.54

Continuous data are presented as mean ± SEM.

Table 4
Prevalence of paravalvular regurgitation on transesophageal echocardiograms after transcatheter aortic valve implantation (TAVI)

Variable	Paravalvular AR		
	None (n = 23)	Grade 1 (n = 47)	Grade 2 (n = 9)
Wall of left cusp	51 (10.8%)	25 (5.3%)	3 (0.6%)
Wall of right cusp	61 (12.9%)	16 (3.4%)	2 (0.4%)
Wall of noncoronary cusp	43 (9.1%)	33 (7.0%)	3 (0.6%)
Left–right commissure	70 (14.8%)	9 (1.9%)	0
Left–noncoronary commissure	74 (15.6%)	3 (0.6%)	2 (0.4%)
Right–noncoronary commissure	73 (15.4%)	6 (1.2%)	0

Data are presented as absolute number of transesophageal echocardiographic sites with or without paravalvular AR (expressed as percentage of 474 potential sites in total); 6 sites in each patient for a total of 474 sites in 79 patients.

verse plane should be seen to bisect the aortic cusps equally, permitting visualization of the insertion points of all 3 aortic cusps at the level of the aortic annulus. Subsequently, by adjusting the level of the transverse plane, the center line should sit in the center of the 3 aortic cusps at the level of aortic sinus (Figure 1). Next, the software automatically displayed the true short axis of the aortic valve in the transverse MPR view (Figure 1). Then, the additional 2 orthogonal curved MPR views were used to define the region of interest (from the LV outflow tract level to the level before the appearance of the coronary ostium). The software then automatically provided AVC quantification and the exact location of calcium (Figure 1). Six locations of calcium were identified on each cusp (Figure 1), and the respective AVC could be quantified in cubic millimeters (Figure 1).

Immediately after prosthesis deployment, the short- and long-axis views of TEE were used to assess the presence of AR and its severity and sites (origins of leak). The severity of AR was assessed qualitatively using color Doppler flow imaging and the maximal jet width at its origin from the prosthesis.[11] AR was graded as follows: 0, absent; 1, trace and mild; 2, mild-to-moderate; 3, moderate-to-severe; and 4, severe.[7,12] In addition, AR was classified as paravalvular or intravalvular, or both. To determine the exact site of origin of paravalvular AR, a short-axis view (30° to 60°) at the level of the proximal (ventricular) end of the implanted prosthesis was used. Accordingly, 6 sites of paravalvular AR were identified using the interatrial septum as a landmark, which helped to identify the noncoronary cusp (Figure 2).

Continuous variables are presented as the mean ± SD or SEM and categorical variables as percentages. Comparisons between patients with and without paravalvular AR after TAVI were performed using unpaired Student's *t* tests (for continuous variables) and the chi-square or Fisher exact test (for categorical variables). To relate the locations of AVC with the sites of paravalvular AR after TAVI using TEE, the locations of AVC with their respective sites of paravalvular AR were matched. Receiver operating characteristic curves were subsequently generated to evaluate the predictive value of the AVC volume in determining paravalvular AR at a specific site. All statistical analyses were performed with the Statistical Package for Social Sciences, version 16.0 (SPSS, Chicago, Illinois). A p value <0.05 was considered statistically significant.

Results

The baseline clinical and echocardiographic characteristics of the study population are presented in Tables 1 and 2. The transfemoral approach was performed in 36 patients

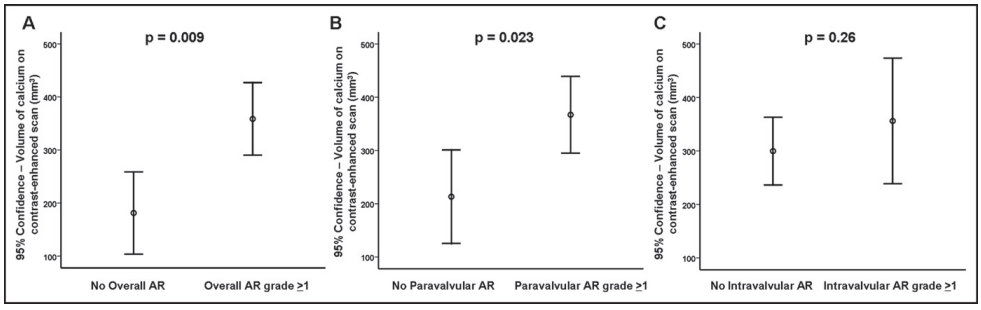

Figure 3. Total volume of baseline AVC on contrast-enhanced multidetector row computed tomographic scans for presence or absence of each type of AR: *(A)* overall, *(B)* paravalvular, and *(C)* intravalvular. Data presented as mean and 95% confidence intervals.

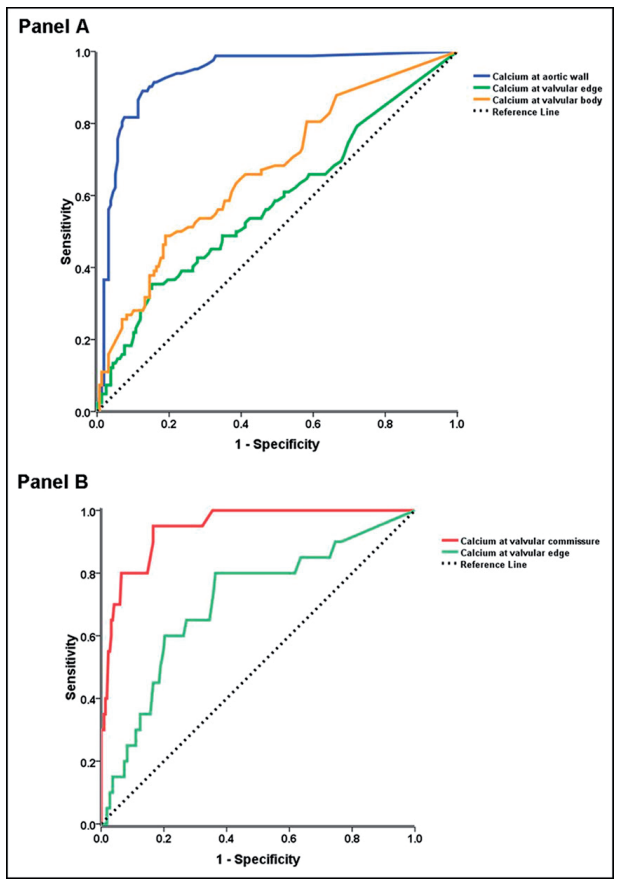

Figure 4. Calcium load and its location as predictor of paravalvular AR at *(A)* aortic wall site or *(B)* commissure site.

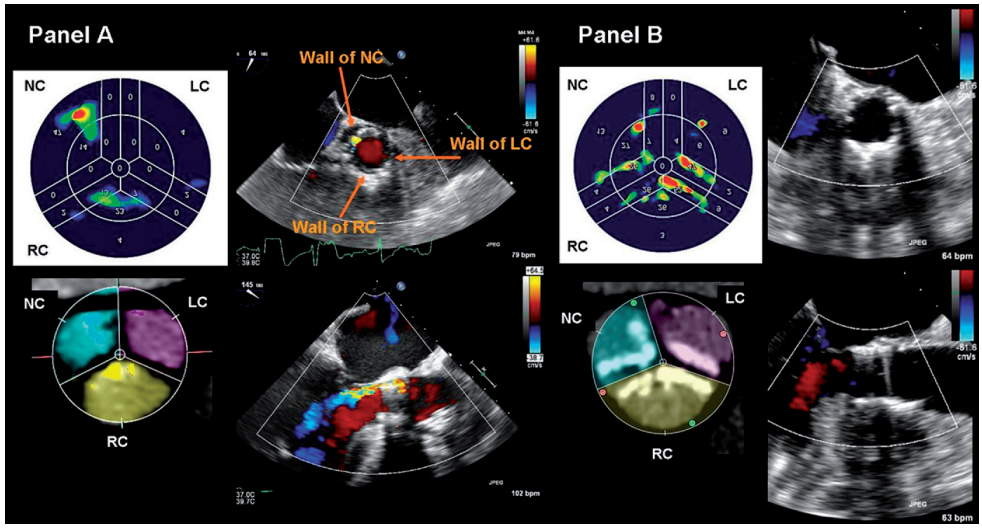

Figure 5. *(A)* Example showing location and volume of AVC on contrast-enhanced multidetector row computed tomographic scan, as provided by automated postprocessing software and subsequent development of paravalvular regurgitation after TAVI. *(B)* Example of patient without paravalvular regurgitation after TAVI showing location and volume of AVC on contrast-enhanced multidetector row computed tomographic scan at baseline. Images of MDCT are rotated for easy comparison with corresponding views on transesophageal echocardiogram. Abbreviations as in Figure 2.

(46%), and the transapical approach in 43. In terms of prosthesis size, 62 patients (78%) received a 26-mm valve and 37 a 23-mm valve. The baseline measurements of the total volume of AVC and volume of calcium on each location of the aortic cusp are listed in Table 3. Because the valvular commissures or valvular free edges were closely related to each other on 2 apposing cusps (Figure 1), they were considered as a unit when AVC was concerned. Hence, the amount of calcium on the valvular commissures or free edges was the summation of their respective volume of calcium on the 2 associated cusps.

Grade 1 or greater AR immediately after initial prosthesis deployment was observed in 63 patients: grade 1 (mild) in 49 (62%), grade 2 (mild-to-moderate) in 11 (14%), and grade 3 (moderate-to-severe) in 1 (4%). The remaining 16 patients (20%) did not have any detectable AR. Severe AR (grade 4) was not observed. In terms of the distribution of AR after TAVI (n = 63), most patients had paravalvular AR (n = 56), and isolated intravalvular AR was observed in a few patients (n = 7). The proportion of patients with and without postprocedural paravalvular AR was comparable among the patients who underwent the transfemoral or transapical approach (45% vs 48% and 55% vs 52%, respectively; p = 0.81) or those who received a 23- or 26-mm prosthesis (21% vs 22% and 79% vs 78%, respectively; p = 1.00).

Among the patients with postprocedural paravalvular AR, 6 potential sites of leakage using TEE in each patient were identified (Figure 2). Hence, the total number of potential sites for the entire population was 474. The prevalence of paravalvular AR at these 6 specified sites is listed in Table 4. The total number of sites with paravalvular AR was 102, and most occurred at the aortic wall sites (82 sites, 80%), with few originating from the valvular commissures (20 sites, 20%).

Patients with a greater AVC volume at baseline had a greater prevalence of AR after TAVI (Figure 3). In particular, the total AVC volume was related to the development of paravalvular AR but not to intravalvular AR after TAVI (Figure 3). Accordingly, the study population was dichotomized into the presence and absence of paravalvular AR to further assess the relation between AVC (and its locations) and the occurrence of paravalvular AR.

To relate the locations of AVC with the presence of paravalvular AR at the 6 specified sites after TAVI, we first matched the locations of AVC with their respective sites of paravalvular AR. For AR originating from the aortic walls (1 from each cusp, 3 sites in total), each AR site was matched with its AVC location on each cusp at the aortic wall, valvular edge, and valvular body, respectively. Next, receiver operating characteristic curves were generated to determine the usefulness of the volume of calcium on its respective AVC location in predicting the presence of paravalvular AR (originating from the aortic wall site). As demonstrated in Figure 4, calcium at the aortic wall had the largest area under the curve (0.93, p <0.001) in predicting the occurrence of paravalvular AR (at the aortic wall site)

compared to calcium at the valvular edge or body (area under the curve 0.58 and 0.67, respectively).

Similarly, for AR originating from the commissures (3 sites in total), each site was matched with its corresponding AVC location on the valvular commissure and the respective valvular edge involved: the left–right, left–noncoronary, and right–noncoronary, respectively. Figure 4 shows that calcium at the valvular commissure had a greater area under the curve than calcium at the valvular edge (0.94 vs 0.71) in predicting the occurrence of paravalvular AR originating from the commissures. Figure 5 shows examples of a grade 1 paravalvular AR and no AR after TAVI and their respective locations and severity of AVC.

Discussion

The present study highlighted that both the amount of calcium and its exact location on the aortic valve are important in determining the development of paravalvular AR after TAVI. The amount of calcium at the aortic wall was the main determinant of subsequent paravalvular AR at the corresponding aortic wall site, and the amount of calcium at the valvular commissure could predict the occurrence of subsequent paravalvular AR, originating from the corresponding commissure.

Previous studies have shown that AVC can be objectively quantified using electron beam computed tomography and MDCT.[13–16] In addition, differing amounts of calcium on the surfaces of the cusps have been observed in excised stenotic aortic valves.[17] Recent studies that focused on the role of AVC and its relation to post-TAVI AR[1,8,13] have been performed using the Agatston score. However, the volumetric calcium scoring method has been shown to improve interscan reproducibility compared with the Agatston score.[9,10,16] Using only unenhanced MDCT, visualization of the valve leaflets can be challenging. Therefore, contrast-enhanced MDCT is commonly performed for better visualization of AVC and its precise location on the aortic valve.[1,2] The present study demonstrated the feasibility of volumetric quantification of AVC, together with its detailed location on the aortic valve, using the automated postprocessing software using contrast-enhanced MDCT.

Although dramatic improvement has occurred in the periprocedural complication rate in the recent TAVI series,[18–20] there is still a significant proportion of patients (72% to 84%) with at least some degree of paravalvular AR after TAVI.[18,21] This is consistent with the results of the present study, which showed that 71% of patients had paravalvular AR. The long-term effect of AR, however mild it might be, is yet to be determined. A few recent studies have alluded to the importance of AVC severity in the development of AR after TAVI.[1,2,8] In a recent study of 57 patients who underwent TAVI (balloon-expandable valves in 33% and self-expanding valves in 67%), Koos et al[2] showed that the severity of AR after deployment was positively related to AVC severity. In addition, John et al[1] demonstrated in 100 patients with self-expanding valve implantation that although a significant relation exists between total calcium at the device landing zone and the grade of paravalvular AR after deployment, this relation was weak ($r = 0.33$, $p = 0.001$). Therefore, the study by John et al[1] suggested that the location of AVC might be more important than the total amount of AVC in determining AR after TAVI.

In the present study, we have confirmed the relation between the location of AVC and the presence of paravalvular AR, the predominant type of AR observed after TAVI. More importantly, we have shown that the main determinant of any detectable paravalvular AR, originating from the aortic wall site, was the amount of calcium at the corresponding aortic wall. Calcium at other locations such as the valvular edge or body was less important in determining the presence of paravalvular AR arising from the aortic wall site. When paravalvular AR originating from the commissure was analyzed, the main determinant of any detectable AR was the amount of calcium at the corresponding commissure of the native valve. Therefore, the results of the present study have highlighted the important role of both the AVC load and its location, in predicting the development of paravalvular leakage after TAVI. Although the mechanism is not entirely clear, the most likely explanation is that the calcified, native aortic valve is pushed outward toward the walls of the aorta initially during ballooning and later, by the balloon expandable bioprosthesis (which has a height of 14 to 16 mm).[22] Therefore, when a significant amount of calcium is present at the circumference of the native valve, it can potentially prevent perfect apposition between the prosthesis and aortic walls and, thus, result in paravalvular AR at these sites. These results suggest that extra caution should be given to patients, particularly those with calcium at the circumference of the native aortic annulus, and perhaps, additional maneuvers such as prolonged ballooning or reballooning might be necessary when paravalvular AR is present after deployment.

We acknowledged that this was a relatively small study and that it was insufficient to study the clinical end points of at least moderate AR after TAVI. This will need to be explored in a larger population.

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Effect of aortic regurgitation following transcatheter aortic valve implantation on outcomes

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Effect of Aortic Regurgitation Following Transcatheter Aortic Valve Implantation on Outcomes

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The prognosis of aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) and the changes in AR grade over time remain unclear. This study evaluated the midterm survival associated with AR after TAVI and examined the evolution of AR over time and its effect on cardiac performance. Successful TAVI was performed in 314 patients (age 81 ± 7 years, 36% men). Serial transthoracic echocardiography and clinical assessment were available in 175 patients who survived >12 months. AR was assessed in terms of overall, paravalvular, and intravalvular severity. Significant post-TAVI AR (grade ≥2) was observed in 82 patients (26%), and these patients showed a trend toward reduced survival at 1- (93% vs 91%) and 2-year (89% vs 74%, log-rank p = 0.063) follow-up. Of the 175 patients who survived >12 months, grade ≥2 overall, paravalvular, and intravalvular AR were noted in 47 (27%), 32 (18%), and 8 patients (5%), respectively. Significant overall and paravalvular AR appeared to improve over time, particularly during the first 6 months (p <0.05), whereas intravalvular AR remained unchanged. Although improvements in the echocardiographic parameters were similar among patients with and without significant AR, patients who remained with grade ≥2 AR at 6 months had significantly worse survival than their counterparts at 2 years (80% vs 94%, log-rank p = 0.032). In conclusion, significant overall and paravalvular AR after TAVI appeared to improve over time. Although improvements in the echocardiographic parameters were similar, patients with grade ≥2 AR, both immediately after TAVI and at 6 months, were associated with worse survival. **© 2015 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2015;115:664−669)**

Transcatheter aortic valve implantation (TAVI) is an established alternative therapy for patients with symptomatic severe aortic stenosis (AS) who are deemed to have high risk or contraindications for conventional surgery.[1] Although advances in technical devices and proper patient selection have significantly improved TAVI results,[2,3] aortic regurgitation (AR) remains a common finding after TAVI. Moreover, significant AR after TAVI has been associated with an increase in in-hospital mortality and less favorable clinical outcomes.[2,4−6] However, the changes in post-TAVI AR during follow-up and its effect on long-term clinical outcomes remain to be clarified. Therefore, the aim of the study was twofold: first, to evaluate the midterm survival associated with AR after TAVI; and second, to examine the evolution of AR over time and its effect on cardiac performance and outcomes at mid- and long-term follow-up.

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See page 669 for disclosure information.

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Methods

Patients with symptomatic severe AS who underwent successful TAVI at Leiden University Medical Center, Leiden, the Netherlands, and Centro Cardiologico Monzino, IRCCS, Milan, Italy, were included. All patients had severe AS, defined as an aortic valve area <1 cm^2 or <0.6 cm^2/m^2, and were considered at high risk or had contraindications for conventional valve surgery. All consecutive patients with successful TAVI procedures who survived the index hospitalization, from November 2007 to March 2011, were included. Patients with bicuspid aortic valves or previous aortic or mitral prostheses were excluded. For the subsequent analysis, which aimed at evaluating the changes over time of AR after TAVI and its effect on cardiac hemodynamics and clinical outcomes, patients with a follow-up duration of at least 12 months after implantation were included. According to the institutional protocols, all patients underwent clinical and echocardiographic evaluation at baseline, after the procedure (before hospital discharge), at 6 months, and then annually. Clinical and echocardiographic data were prospectively recorded and subsequently analyzed. All patients received either the 23- or 26-mm balloon-expandable Edwards-SAPIEN valves (Edwards Lifesciences, Inc., Irvine, California) depending on the diameter of the aortic annulus.[7] Only 2 patients received the 29-mm valve. The device was delivered through either the transfemoral or transapical approach (in patients with unsuitable aortoiliofemoral anatomy).[8]

Table 1
Baseline patient characteristics

Variable		Patients (n=314)
Age (years)		81.2±6.5
Men		114 (36%)
Body surface area (m^2)		1.72±0.20
Logistic EuroSCORE (%)		20.5±11.4
Systolic blood pressure (mmHg)		129±20
Diastolic blood pressure (mmHg)		71±10
NYHA functional class	II	80 (26%)
	III	172 (55%)
	IV	62 (20%)
Previous myocardial infarction		62 (20%)
Previous coronary bypass surgery		63 (20%)
Previous percutaneous coronary intervention		80 (26%)
Peripheral vascular disease		126 (40%)
Hypertension*		255 (81%)
Hypercholesterolaemia*		165 (53%)
Diabetes mellitus		88 (28%)
Hemoglobin (g/dL)		12.0±1.6
Heart rhythm	Sinus	238 (77%)
	Atrial fibrillation	53 (17%)
	Paced	23 (7%)
Frailty		75 (24%)
Aortic valve area (cm^2)		0.68±0.17
Mean transaortic gradient (mmHg)		48±16
Left ventricular ejection fraction (%)		54.8±12.5
Approach	Transfemoral	171 (55%)
	Transapical	143 (46%)

Continuous data are presented as mean+SD and categorical data as n (%).
* Hypertension: history of high blood pressure and/or on antihypertensive treatment. Hypercholesterolemia: history of hypercholesterolemia and/or on statin therapy.

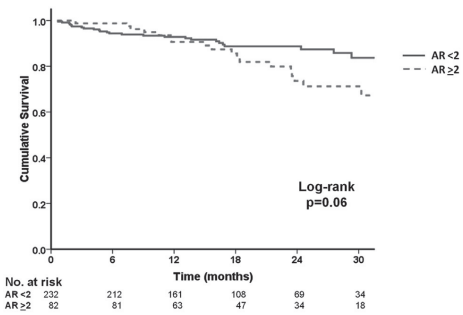

Figure 1. Survival Kaplan-Meier curves for patients with post-TAVI AR grade ≥2 or <2 before hospital discharge.

Standard 2-dimensional, color and Doppler transthoracic echocardiography was performed in all patients at baseline, after the procedure (before hospital discharge), at 6 months, and annually, using a commercially available ultrasound system (Vivid-7; General Electric, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC, version 110.0.0; GE-Vingmed, Horten, Norway). The left ventricular (LV) outflow tract, aortic annulus diameters, and transaortic gradient were measured, as recommended, and aortic valve area was calculated using the continuity equation.[9,10] Standard LV dimensions were obtained, and LV mass index was calculated according to Devereux et al and corrected for body surface area.[9,11] Using the biplane Simpson's method, LV end-diastolic and end-systolic volumes and maximal left atrial (LA) volumes were measured, and LV ejection fraction was derived.[9]

The presence of AR of the native aortic valve at baseline was assessed using color Doppler recordings as recommended.[12] To evaluate the presence and severity of AR after TAVI, a combination of the qualitative and semiquantitative parameters was used according to the current guidelines, after optimizing gain and Nyquist scale (50 to 60 cm/s).[13,14] For intravalvular AR, similar method for assessment of native valvular regurgitation (in terms of ratio of the regurgitant jet to the LV outflow tract width) was applied: <25% mild, 26% to 64% moderate, and >65% severe.[13,14] For paravalvular AR, the proportion of the circumference of the prosthesis occupied by the jet allowed semiquantitative assessment of its severity as described: <10% mild, 10% to 20% moderate, and >20% severe.[13,15] Finally, the assessment of overall AR severity involved integration of all these parameters and was graded as follows: grade 0 (none), grade 1 (mild) when either intravalvular or paravalvular AR was mild, grade 2 (mild to moderate) when both mild intravalvular and mild paravalvular AR were present or when either intravalvular or paravalvular AR was moderate, grade 3 (moderate to severe) when both moderate intravalvular and moderate paravalvular AR were present, and grade 4 (severe) when either intravalvular or paravalvular AR was severe. Significant AR after TAVI was defined as overall AR grade ≥2.

Before hospital discharge and at 6 months, and annually, clinical evaluation was performed, including the classification of heart failure symptoms according to the New York Heart Association functional class. All adverse events[15] and mortality were recorded.

Continuous variables are presented as mean ± SD. Categorical variables are presented as percentages. Preprocedural and follow-up data were compared between patients with (AR grade ≥2) and without significant AR (AR grade <2). Unpaired Student *t* test, chi-square test, or Fisher's exact test was used to compare continuous or categorical variables, as appropriate. In addition, the survival rates are presented as Kaplan-Meier curves, and the log-rank test was used for comparisons between patients with and without significant AR. To examine the changes in AR severity over time, the nonparametric Friedman test for repeated measures was used, followed by post hoc analyses for significant results using a paired Wilcoxon analysis. Finally, repeated-measures analysis of variance was used to evaluate the repeated echocardiographic variables (at different time points), followed by post hoc analyses for significant results using Bonferroni correction. A 2-tailed probability value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows, version 16 (SPSS Inc., Chicago, Illinois).

Results

Baseline clinical characteristics of the 314 patients (age 81 ± 7 years, 36% men) are summarized (Table 1). Post-TAVI AR (before hospital discharge) was observed in 237

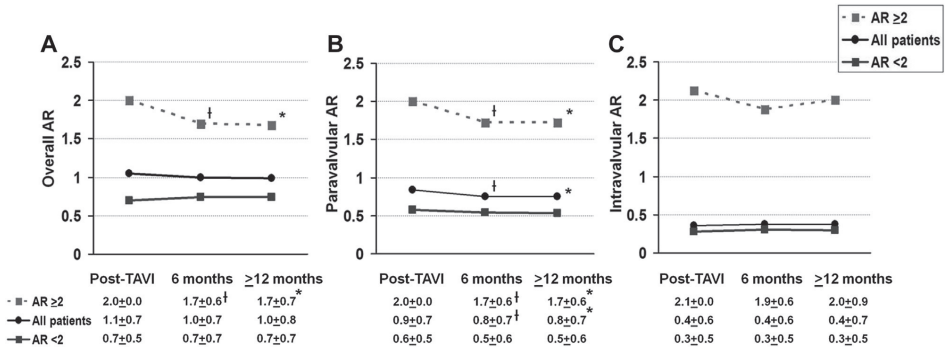

Figure 2. Comparison of changes in the overall *(A)*, paravalvular *(B)*, and intravalvular *(C)* AR severity after TAVI in the entire population, in patients with (grade ≥2) and without (grade <2) significant post-TAVI AR. AR severity at the corresponding time point was given as mean ± SD below each graph. *p <0.05 by the Friedman test. Post hoc test: †p <0.05 between after TAVI and 6 months.

Table 2
Baseline clinical and echocardiographic characteristics in patients with and without significant aortic regurgitation post-transcatheter aortic valve implantation

Variable		Aortic Regurgitation		p-value*
		≥2 (n=47)	<2 (n=128)	
Age (years)		81.3±5.4	80.5±6.9	0.43
Men		21 (45%)	43 (34%)	0.22
Body surface area (m^2)		1.75±0.22	1.73±0.19	0.62
Logistic EuroSCORE (%)		22.5±12.8	19.7±10.6	0.62
NYHA functional class	II	8 (17%)	34 (27%)	0.24
	III	25 (53%)	69 (54%)	
	IV	14 (30%)	25 (19%)	
Previous myocardial infarction		11 (23%)	25 (20%)	0.64
Previous coronary bypass surgery		8 (17%)	29 (23%)	0.53
Previous percutaneous coronary intervention		13 (28%)	34 (23%)	1.00
Peripheral vascular disease		16 (34%)	53 (41%)	0.49
Hypertension		38 (81%)	100 (78%)	0.84
Hypercholesterolaemia		22 (47%)	62 (48%)	0.87
Diabetes mellitus		14 (29%)	30 (23%)	0.43
Hemoglobin (g/dL)		12.0±1.3	12.1±1.7	0.60
Aortic valve area (cm^2)		0.70±0.15	0.70±0.17	0.22
Mean transaortic gradient (mmHg)		48±17	48±16	0.91
Aortic annulus (cm)		22.0±1.8	21.6±1.9	0.17
Left ventricular end-diastolic volume index (ml/m^2)		69±29	62±20	0.25
Left ventricular end-systolic volume index (ml/m^2)		34±24	29±18	0.20
Left ventricular ejection fraction (%)		53±12	56±13	0.25
Left ventricular mass index (g/m^2)		163±55	144±37	**0.03**
Left atrial volume index (ml/m^2)		57±17	51±19	0.11
Aortic regurgitation pre-TAVI	Grade 0-1	33 (70%)	93 (73%)	0.85
	Grade 2-3	14 (30%)	35 (27%)	
Prosthesis size	23 mm	19 (40%)	51 (40%)	1.00
	26 mm	28 (60%)	77 (60%)	

Continuous data are presented as mean+SD and categorical data as n (%).
* p value for comparison between aortic regurgitation ≥2 and <2 using unpaired t test or chi-square test.

patients (76%). AR was classified as none in 77 (25%), grade 1 in 155 (49%), and grade 2 in 81 patients (26%). Only 1 patient (0.3%) had moderate-to-severe AR (grade 3) at the end of the procedure despite reballooning. Significant AR after TAVI, defined as AR grade ≥2, was observed in 82 patients (26%). Over a mean follow-up of 19 months (median 18, 25th to 75th percentile 10 to 28), the overall survival rates at 6 months, 1 year, and 2 years were 96%, 92%, and 84%, respectively. There were a total of 43 deaths: 18 (22%) in patients with post-TAVI AR grade ≥2 and 25 (11%) in patients with post-TAVI AR grade <2. Importantly, there was a trend toward a reduced survival in patients with post-TAVI AR grade ≥2 compared with patients without significant AR, at 1 year (93% vs 91%) and at 2 years (89% vs 74%, log-rank p = 0.06; Figure 1).

To evaluate the changes over time of AR after TAVI, complete echocardiographic data were available in 175 patients who survived at least 12 months. Post-TAVI AR was present in the majority (n = 136, 78%). The overall AR was considered grade 1 in 89 (51%) and grade 2 in 47 patients (27%). In the presence of post-TAVI AR, paravalvular AR was the most common (83%), whereas intravalvular AR was less frequent (42%), with 25% of patients having both AR. The evolution of overall, paravalvular, and intravalvular AR severity was compared before discharge, at 6 months, and ≥12 months after TAVI. No significant change in the overall AR was observed over time (Friedman p = 0.37; Figure 2). Of note, paravalvular AR appeared to improve (Friedman p = 0.014; Figure 2), whereas intravalvular AR was unchanged over time (Friedman p = 0.95; Figure 2).

When the population was analyzed according to the presence or absence of significant post-TAVI AR, marked improvement in the overall AR was observed in patients with overall AR grade ≥2 (n = 47, Friedman p <0.001) with a significant change noted between after TAVI and at 6 months, which was stable over time (Figure 2). In contrast, patients with overall AR grade <2 (n = 128) did not show any change over time (Figure 2). Concerning paravalvular

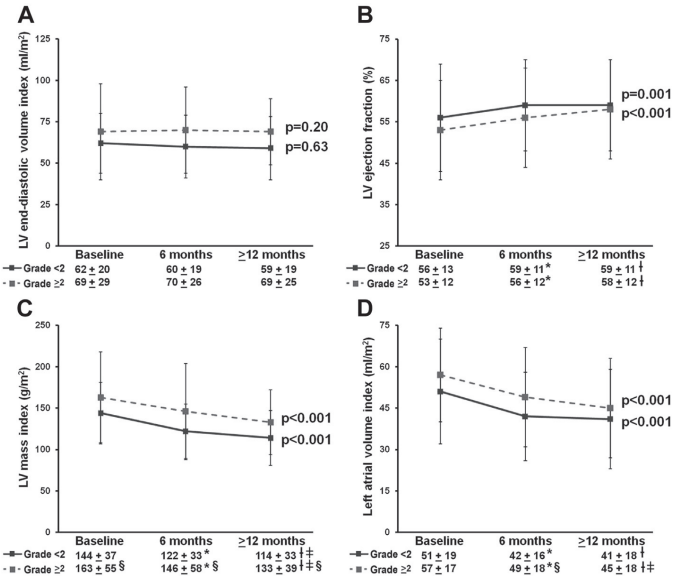

Figure 3. Comparison of changes in LV end-diastolic volume index *(A)*, LV ejection fraction *(B)*, LV mass index *(C)*, and left atrial volume index *(D)* in patients with (grade $\geq$2) and without (grade <2) significant post-TAVI AR. Measurement values (mean $\pm$ SD) at the corresponding time point are given below each graph. p Value by repeated measures of variance. Bonferroni post hoc test: *p <0.05 between baseline and 6 months. †p <0.05 between baseline and $\geq$12 months. ‡p <0.05 between 6 and $\geq$12 months. §p <0.05 between AR grade <2 and $\geq$2.

AR, no significant change in paravalvular AR was observed over time in patients with post-TAVI paravalvular AR grade <2 (n = 143). Importantly, in patients with post-TAVI paravalvular AR grade $\geq$2 (n = 32), significant improvement in paravalvular AR was observed (Friedman p = 0.002), particularly during the first 6 months (Figure 2). Concerning intravalvular AR, most patients had no significant intravalvular AR (n = 167), whereas significant intravalvular AR was present in only 8 patients. Of note, intravalvular AR remained stable, with no significant changes observed over time, regardless of intravalvular AR grade $\geq$2 or <2 (Figure 2). In terms of absolute number of patients, worsening in post-TAVI AR from AR grade <2 to $\geq$2 over time was uncommon (n = 7, 4%). Only 4 patients with mild paravalvular AR developed moderate AR at 6 months, which remained stable thereafter. Among the 3 patients with mild intravalvular AR, 2 patients progressed to moderate AR, while 1 patient developed severe intravalvular AR (from endocarditis) by 6 months. In patients with post-TAVI paravalvular AR grade $\geq$2 (n = 32), notably 9 patients (28%) had reduction in AR to none or mild AR, while only 1 patient (3%) developed severe AR because of endocarditis at 6 months. In contrast, among those with post-TAVI intravalvular AR grade $\geq$2 (n = 8), AR remained unchanged in the majority (n = 7, 88%), and 1 patient (1%) developed severe AR by 6 months, requiring surgery.

To evaluate the hemodynamic effect of significant post-TAVI AR in the subgroup of 175 patients, the echocardiographic variables at 6 and $\geq$12 months were compared. Table 2 summarizes the baseline clinical and echocardiographic characteristics of patients with post-TAVI AR grade $\geq$2 (n = 47) and AR grade <2 (n = 128). During follow-up, no significant changes in LV end-diastolic volumes were observed in both groups (Figure 3). Importantly, patients with post-TAVI AR grade $\geq$2 did not exhibit a significant increase in LV end-diastolic volume over time. Of note, a significant improvement in LV ejection fraction was observed in both groups (Figure 3). Although patients with post-TAVI AR grade $\geq$2 had a larger LV mass at baseline, both groups showed significant LV mass regression over time. In fact, LV mass regression was noted at 6 months and continued to regress beyond 12 months (Figure 3). Similar reduction in LA volume was also observed in both groups over time (Figure 3). In terms of transvalvular hemodynamics, significant improvement in mean gradient and aortic valve area was noted at 6 months for patients with AR grade $\geq$2 (48 $\pm$ 17 vs 12 $\pm$ 7 mm Hg and 0.70 $\pm$ 0.15 vs 2.09 $\pm$ 0.53 cm^2) and with AR grade <2 (48 $\pm$ 16 vs 11 $\pm$ 4 mm Hg and 0.70 $\pm$ 0.17 vs 1.97 $\pm$ 0.43 cm^2), respectively. The majority of patients (n = 166, 95%) reported an improvement in New York Heart Association functional class by $\geq$I class, compared with baseline. However, 6 patients (13%) with post-TAVI AR grade $\geq$2 (n = 47) compared with only 3 patients (2%) with post-TAVI AR grade <2 (n = 128) reported no improvement in functional class.

Given that significant changes in AR occurred within 6 months after TAVI, the effect of significant AR at 6 months on survival was further examined in this group (n = 175).

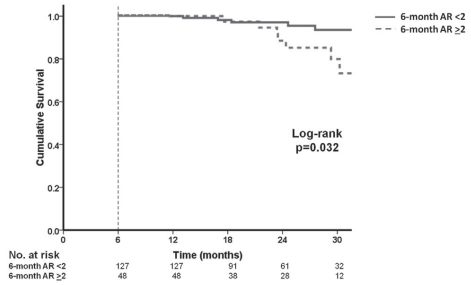

Figure 4. Survival Kaplan-Meier curves for patients with 6-month AR ≥2 or AR <2 after TAVI.

Forty-eight patients (27%) had significant 6-month AR grade ≥2. Over a mean follow-up of 25 months (median 24, 25th to 75th percentile 18 to 30), more deaths were observed in patients with 6-month AR grade ≥2 (n = 7, 15%) than in patients with 6-month AR grade <2 (n = 5, 4%). A significant reduction in survival was noted in patients with 6-month AR grade ≥2 compared with those without significant 6-month AR (n = 127) at 1 year (97% vs 98%) and at 2 years (80% vs 94%, log-rank p = 0.032; Figure 4).

Discussion

The present study showed that significant AR is common immediately after TAVI and that patients with AR grade ≥2 tended to have a less favorable clinical outcome. However, significant AR after TAVI, and in particular paravalvular AR, appeared to improve during the first 6 months after implantation. Interestingly, improvement in LV ejection fraction, together with LV mass regression and LA volume reduction, was similar among patients with and without AR grade ≥2. Nevertheless, patients who remained with AR grade ≥2 at 6-month follow-up showed significantly worse survival than patients with AR grade <2.

Trivial or mild AR, particularly paravalvular, is common and often an acceptable finding after TAVI because of incomplete annular sealing of the transcatheter valve within a calcified aortic valve.[3,4] Recently, there is a growing interest in the effect of AR on outcomes after TAVI.[2,5,6] In their series, Abdel-Wahab et al[5] showed that patients with AR grade ≥2 had a significantly higher in-hospital mortality than those with no or mild AR after TAVI. Because early in-hospital mortality is mainly determined by procedural complications,[2] the present study, therefore, focused on patients who survived the TAVI procedures and examined the midterm all-cause mortality associated with AR. A strong trend toward reduced survival among patients with post-TAVI AR grade ≥2 was observed. This is consistent with recent studies that identified presence of moderate or severe post-TAVI AR as an independent predictor of survival at 1 year[2,6] The Placement of Aortic Transcatheter Valves A trial further confirmed that the effect on mortality at 2 years was proportional to post-TAVI AR severity, even when AR was only mild.[4] These observations underscore the importance of reducing AR to a minimum after TAVI.

Currently, it is still unclear how post-TAVI AR evolves over time. This study observed that paravalvular AR appeared to diminish in severity over time. Importantly, significant paravalvular AR (grade ≥2) after TAVI appeared to improve, particularly within the first 6 months. In a 3-year follow-up study with balloon-expandable valves, patients with moderate AR after TAVI reported improvement to mild AR or remained unchanged by 6 months, although the components of AR were not described.[16] A possible explanation for the progressive reduction in paravalvular AR after balloon-expandable valve implantation is the presence of positive remodeling of the aortic annulus.[17] Over time, the stented prosthesis may adapt to better accommodate and seal the calcified native commissures and thus, minimizing the paravalvular leak.

There are limited data regarding the effect of AR on cardiac performance after TAVI. Although significant AR after TAVI is associated with worse clinical outcomes,[2,5,6] the direct causal relation between AR and mortality remains to be determined, and it is unclear if this is mediated by its hemodynamic consequences on the LV or by other mechanisms associated with noncardiovascular events.[18] In patients with severe AS, the stiff and hypertrophied LV has adapted to the long-standing pressure overload state and is associated with impaired relaxation and elevated LV end-diastolic pressure.[19] Accordingly, when AR develops after TAVI, there is a concern that the AR volume may precipitate a further increase in the already elevated LV end-diastolic pressure, resulting in acute pulmonary edema or inducing LV dilatation in the midterm. This study confirmed that LV ejection fraction improved, accompanied by LV mass regression in both groups of patients (AR grade ≥2 and <2) after TAVI. Interestingly, LV volumes did not increase over time in patients with significant AR, suggesting that the derived hemodynamic benefit of TAVI after the relief of AS still outweighed the perceived negative effect of AR after TAVI, at least at midterm follow-up. In a 5-year follow-up of 84 patients with surgical aortic valve, Rallidis et al[20] also reported that LV dimensions did not differ in patients with or without paravalvular leak, whereas the wall thickness decreased and fractional shortening increased in both groups.

Although significant AR was not associated with overt harmful effect on LV structure and function on echocardiography, its undesirable effects on clinical outcomes should not be overlooked. More patients with significant post-TAVI AR reported no improvement in functional class, compared with patients with AR grade <2 in this study, which is consistent with the study by Gotzmann et al,[21] that identified moderate and severe AR as an independent predictor of no improvement of functional class at 6 months. Moreover, the present study highlighted that patients with significant AR that persisted at 6 months were also associated with worse survival (Figure 4). In comparison with previous studies that focused on post-procedural AR and its negative effect on early survival,[2,4–6] this study observed the negative association between significant AR at 6 months after TAVI and late survival. Other mechanisms that are beyond the scope of this study may be responsible for the poor outcomes, such as undesirable neurohumoral changes, impaired coronary flow, and possible higher risk of hemolysis.

We acknowledge that inclusion of only patients who survived at least 12 months may have limited the ability to

draw definite conclusion. However, the aim of the study was to examine how AR after TAVI changes over time, and this could only be studied in patients who survived a period of time after the procedure and underwent systematic echocardiographic examination. Moreover, transthoracic Doppler echocardiography only provides a semiquantitative hemodynamic assessment of AR severity and is subjected to variability and requires further validation.

Disclosures

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Hemodynamic and clinical impact of prosthesis-patient mismatch after transcatheter aortic valve implantation

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Hemodynamic and Clinical Impact of Prosthesis–Patient Mismatch After Transcatheter Aortic Valve Implantation

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Objectives This study examined the mid-term hemodynamic and clinical impact of prosthesis–patient mismatch (PPM) in patients undergoing transcatheter aortic valve implantation (TAVI) with balloon-expandable valves.

Background PPM can be observed after aortic valve surgery. However, little is known about the incidence of PPM in patients undergoing TAVI.

Methods Echocardiography and clinical assessment were performed in 165 patients at baseline, before hospital discharge, and at 6 months after TAVI. PPM was defined as an indexed effective orifice area ≤ 0.85 cm^2/m^2.

Results Thirty patients (18.2%) showed PPM before hospital discharge. At baseline, patients with PPM had a larger body surface area (1.84 ± 0.18 m^2 vs. 1.73 ± 0.18 m^2, $p = 0.003$) and a greater severity of aortic stenosis (indexed valve area 0.35 ± 0.09 cm^2/m^2 vs. 0.40 ± 0.10 cm^2/m^2, $p = 0.005$) than patients without PPM. Patients with PPM demonstrated a slower and smaller reduction in mean transaortic gradient, limited left ventricular (LV) mass regression, and left atrial volume reduction over 6 months compared with patients without PPM. LV filling pressure, measured by E/e′, tended to remain elevated in patients with PPM. Importantly, a higher proportion of patients with PPM did not improve in New York Heart Association functional class compared with patients without PPM (36.7% vs. 1.5%, $p < 0.001$), although major adverse valve-related and cardiovascular events did not differ between the 2 groups.

Conclusions PPM may be observed after TAVI and when present may be accompanied by less favorable changes in transvalvular hemodynamics, limited LV mass regression, persistent elevated LV filling pressure, and less improvement in clinical functional status. (J Am Coll Cardiol 2011;58:1910–8) © 2011 by the American College of Cardiology Foundation

Prosthesis–patient mismatch (PPM) can be observed after surgical aortic valve replacement for severe aortic stenosis (AS) (1–4) when the effective orifice area (EOA) of a normally functioning prosthesis is too small in relation to the patient's body size (5). The presence of significant PPM after aortic valve surgery has been associated with worse transvalvular hemodynamics and limited regression of left ventricular (LV) hypertrophy as a result of increased LV afterload (6). In addition, reduced indexed EOA has been reported to negatively affect clinical outcomes (1–4).

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So far, only a few small series (7–9) have described the incidence of PPM after transcatheter aortic valve implantation (TAVI), and little is known about its impact on LV performance and clinical outcomes in these patients. Therefore, we aimed to evaluate the mid-term hemodynamic and clinical impact of PPM in patients with severe

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AS undergoing TAVI with the balloon-expandable Edwards SAPIEN bioprosthesis (Edwards Lifesciences, Inc., Irvine, California).

Methods

Patient population. A total of 190 consecutive patients with symptomatic severe AS who underwent TAVI at Leiden University Medical Center, Leiden, the Netherlands, and Centro Cardiologico Monzino, IRCCS, Milan, Italy, were included. Based on a multidisciplinary team assessment, all patients had severe AS, defined as an aortic valve area <1 cm^2 or <0.6 cm^2/m^2, and were considered at high operative risk or had contraindications to conventional aortic valve surgery. Patients with previous aortic or mitral prostheses, unsuccessful TAVI, or an echocardiographic follow-up <6 months were excluded from the present analysis.

According to the institutional protocols, all patients underwent clinical and echocardiographic evaluation at baseline, post-procedure (before hospital discharge), and at 6 months follow-up. The incidence of PPM and the hemodynamic and clinical impact of the presence of PPM during follow-up were assessed. Clinical and echocardiographic data were prospectively recorded and retrospectively analyzed.

TAVI procedure. The balloon-expandable Edwards-SAPIEN prostheses (Edwards Lifesciences, Inc.) of either 23 or 26 mm was used in all patients when the aortic annulus was 18 to 22 mm and 21 to 25 mm (as confirmed by transesophageal echocardiography), respectively (10). This valve consists of a trileaflet bovine pericardial tissue valve, mounted within a stainless steel balloon-expandable stent. As previously described (11), the device was delivered via either a transfemoral (retrograde) or transapical (antegrade) approach. The transapical approach was performed in patients with unsuitable aortoiliofemoral anatomy such as iliofemoral arteries <7 to 8 mm, marked tortuosity, abdominal aortic aneurysm, porcelain aorta, and/or previous aortoiliac surgery or intervention (12). All procedures were performed under transesophageal echocardiographic and fluoroscopic guidance.

Transthoracic echocardiography. Transthoracic echocardiography was performed in all patients at baseline, before hospital discharge, and at 6-month follow-up, using a commercially available ultrasound system (Vivid-7, General Electric, Horten, Norway). All images were digitally stored for offline analysis (EchoPAC version 108.1.5, GE-Vingmed, Horten, Norway) and included standard 2-dimensional, color, pulsed, and continuous-wave Doppler acquisitions (13–15). Standard linear LV dimensions were obtained (14), and LV mass was calculated as recommended (14). LV end-diastolic and -systolic volumes were measured from the standard apical views according to the biplane Simpson method (14) and indexed to body surface area (BSA). Next, LV ejection fraction was derived. Similarly, maximal left atrial (LA) volumes were measured using the biplane Simpson method and indexed to BSA (14). Pulmonary artery systolic pressure was estimated from the Doppler spectral signal of tricuspid regurgitation jet (16). The presence of aortic or mitral regurgitation was evaluated using color Doppler, and the severity was assessed according to current guidelines (15).

Abbreviations and Acronyms

AS = aortic stenosis
BSA = body surface area
EOA = effective orifice area
LA = left atrium
LV = left ventricular
LVOT = left ventricular outflow tract
MAVCE = major adverse valve-related and cardiovascular event(s)
NYHA = New York Heart Association
PPM = prosthesis–patient mismatch
TAVI = transcatheter aortic valve implantation

To assess LV diastolic function, transmitral early (E-wave) and late (A-wave) velocities and E-wave deceleration time were measured using pulsed-wave Doppler at the mitral leaflet tips (16). Pulmonary venous flow velocities during systole and diastole were also recorded (16). By integrating transmitral and pulmonary venous flow analysis, diastolic dysfunction was classified as follows: 1) impaired relaxation if mitral E/A <0.8 and pulmonary venous systolic velocity > diastolic velocity; 2) pseudonormal filling if mitral E/A = 0.8 to 1.5, E-wave deceleration time = 160 to 200 ms and pulmonary venous systolic velocity < diastolic velocity; and 3) restrictive filling if E/A ≥2, E-wave deceleration time <160 ms, and pulmonary venous systolic velocity < diastolic velocity (16). In addition, peak early diastolic velocities of the septal mitral annulus (e′) were measured by pulsed wave tissue Doppler imaging from the apical 4-chamber view (16). Then, the ratio of E/e′ was calculated. In patients who were not in sinus rhythm, e′ was used as an additional parameter to help determine the degree of LV diastolic dysfunction: impaired relaxation if e′ <10, pseudonormal filling if e′ <8, and restrictive filling if e′ <5 (17).

The aortic annulus was measured in a zoomed-up parasternal long-axis view as recommended (14). Similarly, the left ventricular outflow tract (LVOT) diameter was measured within 5 to 10 mm into the LVOT from the level of the aortic annulus in mid-systole (13). Pulsed-wave Doppler was used for LVOT measurements and continuous-wave Doppler was used for transaortic measurements. Using the continuity equation (13), the aortic valve area was obtained and indexed to BSA. In patients with sinus rhythm, the 3 best available signals were recorded and averaged. In patients who were not in sinus rhythm, a minimum of 5 measurements was averaged (13).

Definition of PPM after TAVI. After TAVI, the EOA of the prosthesis was similarly calculated using the continuity equation approach. From the parasternal long-axis view in a zoomed mid-systolic frame, the LVOT was measured just below the ventricular end of the prosthesis (but not inside it) to avoid the area of subvalvular flow acceleration. The EOA was subsequently calculated, assuming a circular geometry

of the LVOT, and indexed to BSA. PPM was defined as an indexed EOA ≤0.85 cm^2/m^2 (3,6).

Follow-up data collection. Before hospital discharge and at 6-month follow-up, clinical evaluation included the classification of heart failure symptoms according to the New York Heart Association (NYHA) functional class. In addition, all adverse procedural and in-hospital events and mortality were recorded. In particular, major adverse valve-related events, defined as any structural deterioration or nonstructural prosthesis dysfunction, valve thrombosis, embolism, bleeding event, or valve endocarditis, were recorded (18).

During follow-up, major cardiovascular events, such as death, myocardial infarction, stroke, and heart failure, were recorded. A combined endpoint of major adverse valve-related and cardiovascular events (MAVCE) was used for Kaplan-Meier survival analysis.

Statistical analysis. Continuous variables are presented as mean and SD unless otherwise specified. Categorical variables are presented as frequencies and percentages. Preprocedural and follow-up data were compared between patients with PPM (indexed EOA ≤0.85 cm^2/m^2) and without PPM (indexed EOA >0.85 cm^2/m^2). An unpaired Student *t* test or chi-square test or the Fisher exact test was used to compare continuous or categorical variables, as appropriate. A chi-square test was used to compare categorical variables when no cells had an expected count <5, whereas the Fisher exact test was performed when ≥1 cell had an expected count <5. A 2-way repeated-measures analysis of variance was used to evaluate the effects of time (baseline vs. hospital discharge vs. 6-months follow-up) and the presence or absence of PPM on each echocardiographic variable (EOA, transaortic gradient, LV ejection fraction and mass, LA volume, and E/e′), followed by post hoc analyses for significant results performed using Bonferroni correction with 3 pairwise comparisons. In addition, the interaction between group (presence or absence of PPM) and time was also analyzed for each echocardiographic variable and expressed as group-by-time analysis of variance. Finally, the MAVCE-free survival rates were presented as Kaplan-Meier curves, and the log-rank test was used for comparison between groups. A 2-tailed probability value of <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows version 16 (SPSS Inc., Chicago, Illinois).

Results

Patient population. A total of 190 patients were initially included. Of these patients, 25 patients were excluded for different reasons. Eight patients were excluded due to previous aortic or mitral prostheses, and 4 patients did not have a successful implantation procedure. Nine patients died before 6 months and were subsequently excluded from further analysis. These events were due to in-hospital deaths from massive stroke (n = 1), pulmonary disease (n = 2), heart failure (n = 3), and deaths within 6 months from end-stage lung disease (n = 1), chronic renal disease (n = 1), and myocardial infarction (n = 1). They were unrelated to PPM as none of these patients demonstrated PPM post-TAVI. In addition, a further 4 patients were excluded due to extremely poor acoustic windows and echocardiographic images unsuitable for accurate interpretation. Therefore, a total of 165 patients composed the final study population.

The incidence of PPM (indexed EOA ≤0.85 cm^2/m^2) post-TAVI was 18.2% (n = 30), as assessed by transthoracic echocardiography before hospital discharge. Baseline clinical and echocardiographic characteristics of patients with and without PPM are summarized in Tables 1 and 2. Patients with PPM had a significantly larger BSA (Table 1) (19). In addition, patients with PPM had a greater severity of AS at baseline (indexed aortic valve area 0.35 ± 0.09 cm^2/m^2 vs. 0.40 ± 0.10 cm^2/m^2, p = 0.005) compared with patients without PPM, although the calculated valve areas were not significantly different. There was also a trend toward a smaller LVOT, sinotubular junction, and ascending aorta in patients with PPM. However, the aortic annulus diameter, on which the prosthesis sizing was based, did not differ between the 2 groups (Table 2).

Hemodynamic impact of PPM assessed by echocardiography. Echocardiographic Doppler data at baseline, hospital discharge, and 6-month follow-up are summarized in Figure 1. Per the definition, patients with PPM were characterized by a smaller EOA at discharge and 6-month follow-up compared with those without PPM (Fig. 1A). Accordingly, patients with PPM demonstrated a slower and smaller reduction in mean transaortic gradient post-TAVI, resulting in a higher transvalvular gradient at 6-month follow-up (16 ± 8 mm Hg vs. 10 ± 4 mm Hg, p < 0.001) compared with patients without PPM (Fig. 1B).

Small improvements in LV ejection fraction were noted in both groups of patients with and without PPM post-TAVI, and no significant difference in LV ejection fraction was observed between the 2 groups (Fig. 2A). However, in terms of LV mass regression, patients with PPM had a smaller LV mass regression 6 months post-procedure (with a reduction in LV mass index of −7.2 ± 4.6% vs. −21.1 ± 10.6%, p < 0.001) compared with patients without PPM (Fig. 2B). Similarly, patients with PPM had a smaller reduction in LA volume 6 months post-TAVI (with a reduction in LA volume index of −8.0 ± 9.7% vs. −26.0 ± 10.5%, p < 0.001) compared with patients without PPM (Fig. 2C).

With regard to LV filling pressure, E/e′ remained elevated in patients with PPM at 6 months despite TAVI (Fig. 2D). In contrast, TAVI resulted in the significant reduction of LV filling pressure in patients without PPM (with a reduction in E/e′ of −29.7 ± 7.0% vs. −4.6 ± 21.4%, p < 0.001) (Fig. 2D). When LV diastolic function was analyzed according to diastolic dysfunction grade, a higher proportion of patients without PPM showed improvement in LV diastolic function than those with PPM (47.4% vs. 10%, p < 0.001) (Fig. 3A).

Table 1 Baseline Clinical Characteristics

	PPM (n = 30)	No PPM (n = 135)	p Value*
Age, yrs	77.8 ± 9.8	81.1 ± 6.2	0.084
Male	36.7	39.3	0.84
Body surface area, m^2	1.84 ± 0.18	1.73 ± 0.18	0.003
Body mass index, kg/m^2	26.6 ± 4.0	25.5 ± 5.1	0.25
Logistic EuroSCORE	22.2 ± 9.9	21.9 ± 12.3	0.91
NYHA functional class			
II	23.3	17.0	0.46†
III	56.7	68.2	
IV	20.0	14.8	
Previous myocardial infarction	16.7	16.3	1.00
Previous coronary bypass surgery	23.3	18.5	0.80
Previous percutaneous coronary intervention	10.0	22.2	0.13
Peripheral vascular disease	26.7	28.9	0.82
Hypertension	70.0	75.5	0.62
Hypercholesterolemia	43.3	36.3	0.67
Diabetes	33.3	17.0	0.080
Smoking	20.0	31.1	0.18
Frailty‡	26.7	21.5	0.81
Heart rhythm			
Sinus	80.0	81.5	0.80
Atrial fibrillation	10.0	14.8	0.77†
Pacemaker	10.0	3.7	0.16†
Creatinine clearance, ml/min	46.8 ± 6.0	49.3 ± 21.3	0.57
Hemoglobin, g/dl	11.3 ± 2.5	11.6 ± 2.1	0.53
Approach			
Transfemoral	63.3	46.7	0.11
Transapical	36.7	53.3	
Prosthesis size, mm			
23	50.0	35.6	0.15
26	50.0	64.4	

Values are mean ± SD or %. *p value for comparison between PPM and no PPM using an unpaired *t* test or chi-square test. †p value by Fisher exact test. ‡Frailty assessed according to Fried et al. (19).

NYHA = New York Heart Association; PPM = prosthesis–patient mismatch.

In terms of aortic regurgitation, there was no difference in the proportion of patients with aortic regurgitation grade ≥2 before hospital discharge (13.3% vs. 23.0%, p = 0.33) and at 6-month follow-up (13.3% vs. 28.1%, p = 0.11) in the group with and without PPM. During 6-month follow-up, the presence of PPM did not have a significant effect on aortic regurgitation post-TAVI. The proportion of patients who did (33.3% vs. 29.6%) or did not improve (66.7% vs. 70.4%, p = 0.83) in terms of aortic regurgitation grade was similar in patients with and without PPM. Similarly, mitral regurgitation was not affected by the presence of PPM. Patients with PPM who did (26.7% vs. 25.2%) or did not improve (73.3% vs. 74.8%, p = 0.82) in terms of mitral regurgitation grade was similar to the group without PPM.

Clinical impact of PPM. The majority of patients (n = 152, 92.1%) reported a significant improvement in NYHA functional class at 6 months after TAVI. However, there was a significant proportion of patients with PPM (n = 11, 36.7%) who did not demonstrate an improvement in functional class status. In contrast, among patients without PPM post-TAVI, only a small minority of patients (n = 2, 1.5%) did not show an improvement in functional status (Fig. 3B).

No patients were lost during the follow-up period (mean 17.6 ± 7.0 months) and a total of 18 MAVCE were observed. Three events (10%) occurred in the group with PPM: end-stage lung disease, bleeding event, and infective endocarditis. The remaining 15 events (11.1%) occurred in patients without PPM: 2 deaths (liver cirrhosis, intestinal ischemia), myocardial infarction (n = 3), stroke (n = 2), heart failure (n = 5), and bleeding events (n = 3). Importantly, there was no significant difference between patients with and without PPM in terms of MAVCE (log-rank p = 0.82) (Fig. 4).

Discussion

The present evaluation demonstrated that PPM is rather common and occurred in 18.2% of patients undergoing TAVI with balloon-expandable valves. In particular, pa-

Table 2 Baseline Echocardiographic Characteristics

	PPM (n = 30)	No PPM (n = 135)	p Value*
Aortic valve area, cm^2	0.64 ± 0.16	0.69 ± 0.17	0.096
Aortic valve area index, cm^2/m^2	0.35 ± 0.09	0.40 ± 0.10	0.005
Left ventricular outflow tract, cm	19.8 ± 2.1	20.4 ± 1.9	0.065
Aortic annulus, cm	21.2 ± 2.1	21.9 ± 2.2	0.15
Aortic sinus, cm	32.7 ± 4.7	32.7 ± 4.1	0.99
Sinotubular junction, cm	26.0 ± 4.0	27.5 ± 4.2	0.067
Ascending aorta, cm	32.0 ± 4.8	33.0 ± 4.2	0.062
Mean transaortic gradient, mm Hg	44 ± 18	49 ± 17	0.081
Left ventricular end-diastolic volume index, ml/m^2	68 ± 31	61 ± 20	0.23
Left ventricular end-systolic volume index, ml/m^2	32 ± 28	27 ± 16	0.13
Left ventricular ejection fraction, %	52 ± 16	55 ± 11	0.30
Left ventricular mass index, g/m^2	149 ± 50	151 ± 38	0.84
Left atrial volume index, ml/m^2	48 ± 11	52 ± 15	0.095
E-wave, cm/s	92 ± 24	92 ± 29	0.96
A-wave, cm/s	96 ± 44	100 ± 33	0.64
Mitral E/A ratio	1.20 ± 0.78	1.02 ± 0.61	0.20
Mitral deceleration time, ms	219 ± 82	222 ± 77	0.86
E′, cm/s	4.4 ± 0.9	4.7 ± 1.1	0.19
E/e′	22.2 ± 8.3	20.6 ± 7.1	0.28
Diastolic function			
Impaired relaxation	30.0	43.0	0.38†
Pseudonormal filling	53.3	45.9	
Restrictive filling	16.7	11.1	
Pulmonary artery systolic pressure, mm Hg	45 ± 7	42 ± 9	0.100
Aortic regurgitation grade			
0	20.0	19.3	0.63†
I	50.0	58.5	
II	26.7	15.6	
III	3.3	6.7	
Mitral regurgitation grade			
0	20.0	13.3	0.57†
I	56.7	53.3	
II	16.7	27.4	
III	6.7	5.9	

Values are mean ± SD or %. *p value for comparison between PPM and no PPM using unpaired *t* test or chi-square test. †p value by Fisher exact test.
PPM = prosthesis–patient mismatch.

tients with PPM were accompanied by less favorable changes post-TAVI compared with patients without PPM, with higher transvalvular gradient, limited LV mass regression, and LA volume reduction, and with persistent elevated LV filling pressures. Finally, more patients reported a lack of clinical improvement in the group with PPM, although the MAVCE-free survival did not differ between the 2 groups.

Incidence of PPM in patients undergoing TAVI. To minimize paravalvular regurgitation and to ensure adequate annular sealing, it is generally recommended that the implanted prosthesis be slightly larger than the native aortic annulus for the currently applied percutaneous systems (20). For example, in the balloon-expandable delivery system of the Edwards SAPIEN valves, the 23-mm valve is used for aortic annulus between 18 and 22 mm, whereas the 26-mm valve is used for aortic annulus between 21 and 25 mm (10,21). Despite these indications, the current study showed that PPM developed before hospital discharge in 18.2% of patients who underwent Edwards SAPIEN valve implantation.

Using the definition of an indexed EOA ≤0.85 cm^2/m^2, the incidence of PPM post-TAVI has been reported to be higher (32% to 39%) in patients who underwent CoreValve implantation (8,9). This difference can be partially explained by the fact that only 1 size of the device (26 mm, the smallest) was available at the time of TAVI in one-fourth of the patients (27%) in the reported series (9). In addition, the differences in prosthesis design may play a role. The Edwards SAPIEN valve is a trileaflet valve mounted on a balloon-expandable stainless stent frame that is 14.5 mm or 16 mm in height (for the 23- or 26-mm valve, respectively) and is implanted intra-annularly (21). Conversely, the CoreValve (designed for supra-annular implantation) has a longer frame of 53 or 55 mm (for the 26- or 29-mm device, respectively), with the lower third sitting within the LVOT

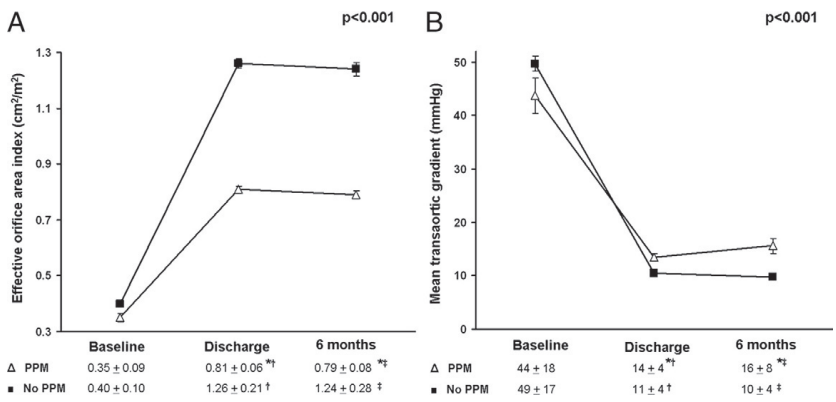

Figure 1 **Impact of PPM on Transvalvular Hemodynamics**

Comparison of changes in aortic effective orifice area index **(A)** and mean transaortic gradient **(B)** in patients with and without prosthesis–patient mismatch (PPM). The p value is for the group-by-time analysis of variance. **Error bars** denote the SEM. Measurement values (mean ± SD) at the corresponding time point are given **below each graph**. *p < 0.05 between PPM and no PPM. Bonferroni post-hoc test: †p < 0.05 versus baseline. ‡p < 0.05 versus baseline.

(21). These differences may account for a potentially higher incidence of PPM with the CoreValve prosthesis. Finally, optimal prosthesis positioning may be important for good expansion and functioning of the transcatheter aortic bioprosthesis. Recently, Jilaihawi et al. (8) reported that a lower incidence of PPM could be achieved with optimal positioning of the prosthesis compared with suboptimal positioning (16% vs. 48%, p = 0.015) in 50 patients who underwent CoreValve implantation.

Of interest, the incidence of PPM has been reported to be lower with the balloon-expandable transcatheter valve compared with surgical bioprosthesis. In a recent matched study of 50 patients who underwent TAVI with an Edwards SAPIEN valve and 2 other groups of 50 patients who underwent surgery with a stented or a stentless bioprosthesis valve (7), the incidence of severe PPM (defined as an indexed EOA ≤ 0.65 cm^2/m^2) was significantly higher in patients with either a stented (26%) or a stentless (28%) bioprosthetic valve than in patients who underwent TAVI (11%). Our findings extended this to a larger population of patients who underwent Edwards SAPIEN valve implantation. The lower incidence of PPM in the TAVI series compared with the surgical series may be partly explained by the absence of a sewing ring and a thinner transcatheter stent frame. Furthermore, sizes of surgical prostheses are generally smaller than transcatheter prostheses, although this might be offset by a routine annular debridement and removal of the native valve before implantation during surgery, which cannot be performed during TAVI (7).

The current study showed that patients with a larger BSA were more prone to the development of PPM post-TAVI. This is probably due to a higher transvalvular flow along with a higher cardiac output required in patients with a larger BSA. Similar findings were observed in the cited study of Jilaihawi et al. (8), including 50 patients who underwent TAVI with a CoreValve prosthesis, in which a larger BSA was observed in patients with PPM compared with patients without PPM (1.8 ± 0.3 vs. 1.7 ± 0.2). It is important to highlight that currently the choice of transcatheter bioprosthesis size depends exclusively on the aortic valve annulus, which was not different between the 2 groups of patients in the present study. These observations suggest that the limited transcatheter prosthesis sizes currently available (for either system) are probably inadequate to avoid PPM, especially in a subset of patients with a larger BSA and taking into account that additional maneuvers, such as removal of the calcified native valve before implantation and root enlargement, cannot be performed. To avoid PPM, a larger selection of transcatheter valve sizes (taking BSA into consideration) and continued improvement of valve design with a better hemodynamic profile (to provide a larger cross-sectional area for blood flow) may be necessary. However, excessive oversizing of the currently used transcatheter prosthesis has to be weighed against the risk of aortic rupture during balloon expansion, especially in patients with a calcified aortic root.

Hemodynamic impact of PPM. In the present study, a marked reduction in the mean transvalvular gradient was observed in all patients post-TAVI, in line with previously reported TAVI series (11). However, this study highlighted that patients with PPM showed less benefit in terms of mean transvalvular gradient reduction compared with patients without PPM. Similar findings have been described

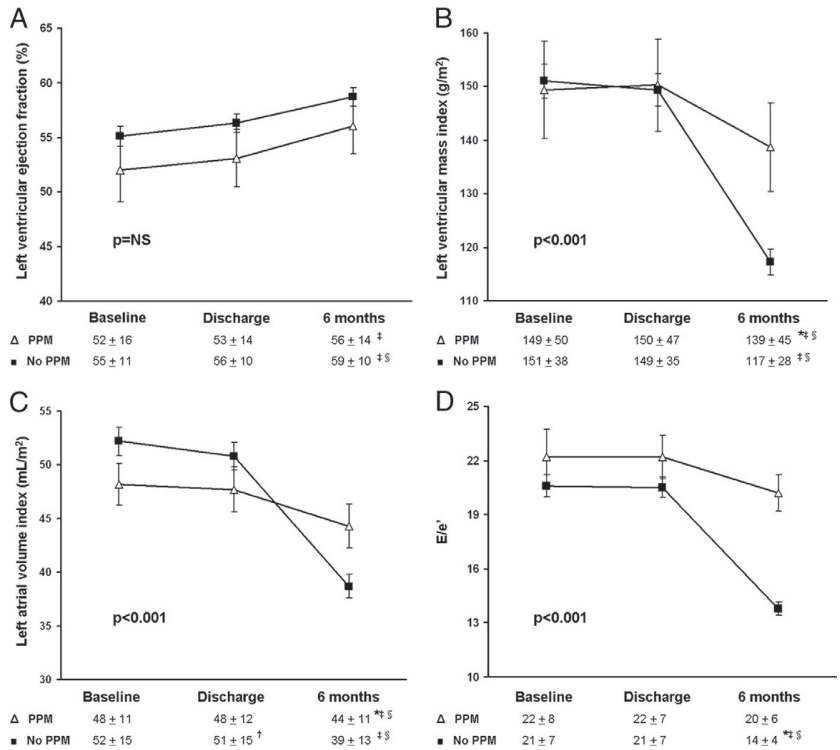

Figure 2 **Hemodynamic Impact of PPM**

Comparison of changes in left ventricular ejection fraction **(A)**, left ventricular mass index **(B)**, left atrial volume index **(C)**, and E/e' **(D)** in patients with and without prosthesis–patient mismatch (PPM). **Error bars** denote the SEM. Measurement values (mean ± SD) at the corresponding time point are given **below each graph**. *$p < 0.05$ between PPM and no PPM. Bonferroni post-hoc test: †$p < 0.05$ versus baseline. ‡$p < 0.05$ versus baseline. §$p < 0.05$ versus discharge.

for patients with PPM with a surgical prosthesis who showed high transvalvular gradient even in the presence of a normally functioning prosthesis (6).

The impact of small indexed EOA and its residual high post-operative gradient on the delay of LV mass regression has been well documented in patients who underwent aortic valve replacement (22,23). Tasca et al. (23) showed that the extent of LV mass regression was related to the extent of the increase in indexed EOA after aortic valve surgery. Similarly, the current study showed that LV mass regression post-TAVI was more pronounced in patients without PPM, whereas in patients with PPM, the regression of LV hypertrophy was less marked (Fig. 2B). This observation might have important clinical implications because regression in LV hypertrophy has been reported to be an important predictor of survival after aortic valve replacement (24). Whether this finding extends to the TAVI population needs to be determined in future studies. In the current study, patients with PPM were observed also to exhibit a more delayed reduction in LA volume and persistently elevated LV filling pressures at 6 months post-TAVI (Fig. 2) compared with patients without PPM. These observations are presumably the result of a combination of incomplete relief of outflow tract obstruction and of a residual significant LV hypertrophy. Ikonomidis et al. (25) previously showed that abnormal LV relaxation was associated with residual LV hypertrophy in patients with isolated AS who had undergone aortic valve replacement. Accordingly, in the present study, only a small proportion (10%) of patients with PPM had improvement in their LV diastolic grades despite the relief of severe AS, whereas more patients without PPM (47%) exhibited a significant improvement in LV diastolic function.

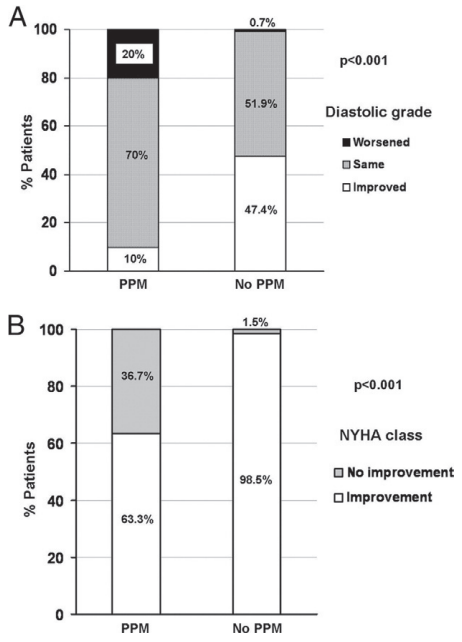

Figure 3 **Impact of PPM on Left Ventricular Diastolic Function and Symptoms**

Comparison of the proportion of patients with changes in left ventricular diastolic dysfunction grade **(A)** and New York Heart Association (NYHA) functional class **(B)** at 6 months after transcatheter aortic valve implantation in patients with and without prosthesis–patient mismatch (PPM). p value denotes the comparison between patients with and without PPM.

Clinical impact of PPM. Another major finding of the present study is that the presence of PPM negatively affected the improvement in NYHA functional class at 6 months post-TAVI. This is in line with previous studies that showed that PPM (defined as an indexed EOA $\leq$0.85 cm^2/m^2) was independently associated with limited improvement NYHA functional class after aortic valve replacement with a stented bioprosthesis (26). In 312 patients who underwent bioprosthetic aortic valve replacement, Bleiziffer et al. (27) also observed that patients without PPM could achieve a better physical exercise capacity compared with patients with PPM. The suboptimal improvements in valvular hemodynamics and the higher residual afterload post-TAVI in patients with PPM could have contributed to the lack of clinical improvement. However, a recent study by Tzikas et al. (9), which included 74 patients who underwent TAVI with the CoreValve, reported that the functional status in terms of NYHA functional class did not differ between patients with (n = 12) and without (n = 62) severe PPM. One of the plausible explanations is that this observation was made by comparing the proportion of patients with NYHA functional class I to II versus III to IV 6 months post-TAVI in the 2 groups (9). Examining the paired changes in NYHA functional class from baseline to 6 months post-TAVI (Fig. 3B) may provide more reliable information on the impact of PPM on an individual patient basis.

So far, there are conflicting reports on the impact of PPM on clinical outcome after aortic valve replacement (1,2,4,28,29). Part of the controversy stems from the use of either the in vitro or the in vivo EOA measurement used to define PPM (5). Nonetheless, using the indexed EOA as a parameter to define PPM, recent series (1–4) demonstrated that patients without significant PPM had better early and late mortality benefits. In addition, patients without PPM exhibit more freedom from congestive heart failure after aortic valve replacement (30). However, the present study showed that there was no significant difference in terms of freedom from MAVCE between patients with or without PPM post-TAVI, which is similar to the finding of a recent series of TAVI using the CoreValve system (9).

Study limitations. Due to a relatively short follow-up period and few major adverse events observed in the present study, the effect of PPM on clinical outcomes will need to be verified in a larger population with a longer follow-up period post-TAVI.

Conclusions

In patients with AS who underwent TAVI with balloon-expandable valves, PPM may be observed. When present,

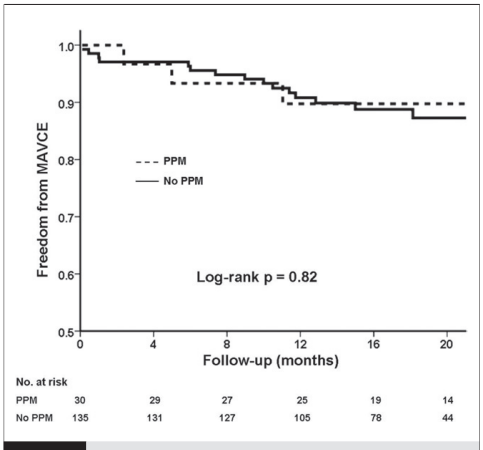

Figure 4 **Kaplan-Meier Curves for Major Adverse Events After Transcatheter Aortic Valve Implantation**

Kaplan-Meier probability of freedom from combined major adverse valve-related and cardiovascular events (MAVCE) in patients with and without prosthesis–patient mismatch (PPM).

PPM may be accompanied by less favorable changes in transvalvular hemodynamics post-TAVI, together with limited LV mass regression and LA volume reduction and with persistent elevated LV filling pressure. More importantly, PPM may be also associated with less functional improvement after TAVI.

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Key Words: aortic valve ■ echocardiography ■ heart valve prosthesis ■ hemodynamics ■ transcatheter aortic valve implantation.

10

Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis

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Impact of left ventricular systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation for severe aortic stenosis

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Background This study aimed to evaluate the impact of baseline left ventricular (LV) systolic function on clinical and echocardiographic outcomes following transcatheter aortic valve implantation (TAVI). Survival of patients undergoing TAVI was also compared with that of a population undergoing surgical aortic valve replacement.

Methods One hundred forty-seven consecutive patients (mean age = 80 ± 7 years) undergoing TAVI in 2 centers were included. Mean follow-up period was 9.1 ± 5.1 months.

Results At baseline, 34% of patients had impaired LV ejection fraction (LVEF) (<50%) and 66% had normal LVEF (≥50%). Procedural success was similar in these 2 groups (94% vs 97%, $P = .41$). All patients achieved improvement in transvalvular hemodynamics. At follow-up, patients with a baseline LVEF <50% showed marked LV reverse remodeling, with improvement of LVEF (from 37% ± 8% to 51% ± 11%). Early and late mortality rates were not different between the 2 groups, despite a higher rate of combined major adverse cardiovascular events (MACEs) in patients with a baseline LVEF <50%. The predictors of cumulative MACEs were baseline LVEF (HR = 0.97, 95% CI = 0.94-0.99) and preoperative frailty (HR = 4.20, 95% CI = 2.00-8.84). In addition, long-term survival of patients with impaired or normal LVEF was comparable with that of a matched population who underwent surgical aortic valve replacement.

Conclusions TAVI resulted in significant improvement in LV function and survival benefit in high-risk patients with severe aortic stenosis, regardless of baseline LVEF. Patients with a baseline LVEF <50% were at higher risk of combined MACEs. (Am Heart J 2010;160:1113-20.)

Symptomatic severe aortic stenosis (AS) is associated with high mortality if left untreated,[1] and surgical aortic valve replacement (SAVR) is currently the recommended therapeutic approach.[2] When severe AS is associated with left ventricular (LV) dysfunction, due to either afterload mismatch[3] or primary myocardial dysfunction, SAVR still results in significant improvement of LV function and survival.[4-6] However, patients with depressed LV ejection fraction (EF) undergoing SAVR are associated with higher perioperative and mid-term mortality[4-8] as compared with those with normal LV systolic function. Furthermore, the combination of LV dysfunction with advanced age and significant comorbidities could result in high predicted operative risk[9] that may outweigh the benefits of SAVR and preclude the surgical intervention.[10]

Over the last few years, transcatheter aortic valve implantation (TAVI) has been proposed as a feasible and effective therapeutic alternative in patients with symptomatic severe AS and high operative risk.[11] In fact, studies have shown excellent and sustained transvalvular hemodynamics post-TAVI,[12] together with a significant improvement in symptoms and quality of life.[12,13] In addition, good survival rates have been reported post-TAVI, ranging from 74% to 78% at the 1-year follow-up.[12,14] However, no studies have examined the impact of baseline LV systolic function on the outcomes of patients undergoing TAVI. Therefore, the aims of this study were:

1. to compare early and long-term clinical outcomes post-TAVI in patients with normal versus impaired LV systolic function;

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2. to evaluate early and long-term changes in LV volumes and function post-TAVI in these 2 groups of patients; and
3. to compare the survival of patients undergoing TAVI with that of a group undergoing SAVR matched for age, gender, aortic valve area, and LVEF.

Methods

Patient population

In total, 147 consecutive patients with symptomatic severe AS who underwent TAVI in 2 centers (Leiden University Medical Center, Leiden, The Netherlands, and Centro Cardiologico Monzino, IRCCS, Milan, Italy) were included. Detailed clinical evaluation, transthoracic echocardiography, and invasive angiography of the coronary/aortoiliofemoral arterial systems were performed in all patients before the procedure.[11] In particular, clinical evaluation included the assessment of operative risk based on the logistic EuroSCORE[9] and identification of associated comorbidities and physical frailty according to the criteria of Fried et al.[15] The decision to offer TAVI to patients was evaluated by a multidisciplinary team approach. All patients underwent clinical and echocardiographic evaluation immediately post-TAVI (within 48 hours) and at the 3-, 6-, and 12-month follow-up points.

The current study received no extramural funding. We, the authors, are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of this article, and its final contents.

Transthoracic echocardiography

Patients were imaged using a commercially available ultrasound system (Vivid-7, General Electric, Horten, Norway). Transaortic pressure gradients and AVA were calculated for all patients.[16] Severe AS was defined as a mean transaortic pressure gradient of at least 40-50 mm Hg or an AVA <1 cm^2.[2] Presence of aortic regurgitation and its severity were evaluated as recommended.[17]

LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were measured and indexed to body surface area.[18] LVEF was derived according to the biplane Simpson method.[18] LV systolic function was defined as normal when LVEF was ≥50% and as impaired when LVEF was <50%.[19] Standard LV ventricular dimensions[18] were also obtained, and LV mass was calculated according to Devereux et al.[18,20]

In addition, LV diastolic function was assessed by the ratio of the transmitral early filling velocity (E wave) to the late diastolic filling velocity (A wave) and the deceleration time of the E wave.[21] Maximal left atrial (LA) area was measured from the standard apical 4-chamber view.[18] Pulmonary artery systolic pressure was calculated as recommended.[21]

TAVI

All patients underwent TAVI with a balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA). The procedures were performed at the catheterization laboratory under general anesthesia with transesophageal echocardiography and fluoroscopy guidance. The prosthesis was implanted via the transfemoral or transapical approach, as previously described.[22] The transapical approach was performed in patients with unfavorable iliofemoral anatomy.[22] Procedural success was defined as implantation of a functioning aortic prosthetic valve without intraprocedural mortality.[12] Duration of fluoroscopy, length of the procedure, and the total contrast volume used during the procedure were also recorded.

Follow-up and data collection

Intraprocedural mortality was defined as any death that occurred before extubation in the catheterization laboratory. Intraprocedural adverse events, such as vascular complication, cardiac tamponade, myocardial infarction, and severe aortic regurgitation, were recorded. The diagnosis of acute myocardial infarction was made on the basis of typical electrocardiographic changes and/or ischemic chest pain associated with elevation of cardiac biomarkers.[23]

In-hospital adverse events, defined as those occurring during the index hospital stay, included all cardiovascular events (such as cardiovascular death, heart failure, stroke, and heart conduction block requiring pacemaker) and noncardiovascular events. Combined major adverse cardiovascular events (MACEs), defined as a composite of death, nonfatal stroke, heart failure, or nonfatal myocardial infarction, were recorded. Total early mortality included both intraprocedural, in-hospital deaths and deaths occurring ≤30 days of the procedure.

No patient was lost to follow-up, and the mean follow-up period was 9.1 ± 5.1 months. Long-term follow-up outcomes included all-cause mortality and major cardiovascular and noncardiovascular-related adverse events.

Statistical analysis

Continuous variables are presented as mean ± SD or as median (interquartile range). Categorical variables are presented as frequencies (percentages). Clinical and echocardiographic characteristics of patients were compared based on LV systolic function (LVEF ≥50% vs LVEF <50%) at baseline.[19] Unpaired Student's *t* test or the Mann-Whitney *U*-test was used to compare the continuous variables, as appropriate. To compare categorical variables, we used χ^2 test or Fisher's exact test, as appropriate. Repeated-measures analysis of variance (ANOVA) was used to analyze the repeated paired continuous variables, and post hoc analysis for significant results was performed using Bonferroni's correction. In addition, survival rates were presented as Kaplan-Meier curves, and the log-rank test was used for comparisons between groups. To identify predictors of cumulative major adverse events after TAVI, we used a Cox proportional hazards model. Variables with $P < .2$ in the Cox univariate analysis were used in the multivariate model. Finally, the survival rate of patients who received TAVI was compared with that of a reference cohort who underwent SAVR in the last 10 years at the Leiden University Medical Center matched for age, gender, AVA, and LVEF. A 2-tailed probability value <.05 was considered statistically significant. All statistical analyses were conducted using SPSS version 16 (SPSS, Chicago, IL).

Results

Baseline characteristics

All patients underwent TAVI due to high operative risk (mean logistic EuroSCORE = 21.8% ± 11.0%) and multiple comorbidities (Table I).

Table I. Baseline clinical and echocardiographic characteristics of patients with a baseline LVEF ≥50% and those with that of <50%

	LVEF ≥50% (n = 97)	LVEF <50% (n = 50)	*P* value*
Age (y)	80.5 ± 6.3	79.8 ± 7.5	.57
Male [n (%)]	35 (36)	28 (56)	.023
Logistic EuroSCORE (%)	20.7 ± 10.6	24.0 ± 11.6	.09
New York Heart Association functional class of III or higher [n (%)]	65 (67)	45 (90)	.002
Previous myocardial infarction [n (%)]	15 (16)	12 (24)	.26
Previous coronary bypass surgery [n (%)]	14 (25)	14 (28)	.69
Previous percutaneous coronary intervention [n (%)]	20 (21)	13 (26)	.53
Peripheral vascular disease [n (%)]	35 (36)	17 (34)	.86
Hypertension [n (%)]	78 (80)	35 (70)	.22
Hypercholesterolemia [n (%)]	45 (46)	27 (54)	.39
Diabetes [n (%)]	17 (18)	20 (40)	.005
Smoking [n (%)]	26 (27)	25 (50)	.006
Frailty [n (%)]†	33 (34)	15 (30)	.71
Heart rhythm			
Sinus rhythm [n (%)]	81 (84)	31 (62)	.007
Atrial fibrillation [n (%)]	16 (17)	14 (28)	.13
Pacemaker [n (%)]	3 (3)	9 (18)	.003
Renal dysfunction [n (%)]‡	18 (19)	12 (24)	.39
Hemoglobin (g/dL)	12.2 ± 1.5	13.7 ± 2.6	.22
Echocardiography			
AVA (cm^2)	0.66 ± 0.16	0.68 ± 0.17	.49
Mean aortic gradient (mm Hg)	52 ± 17	40 ± 15	<.001
LVEDV index (mL/m^2)	56 ± 23	79 ± 27	<.001
LVESV index (mL/m^2)	25 ± 18	47 ± 23	<.001
LVEF (%)	61 ± 7	37 ± 8	<.001
LV mass index (g/m^2)	149 ± 40	174 ± 59	.010
Mitral E/A ratio	0.96 ± 0.73	1.27 ± 0.95	.037
Mitral deceleration time (ms)	244 ± 80	223 ± 93	.017
LA area (cm^2)	23.7 ± 5.7	27.2 ± 6.6	.002
Pulmonary artery systolic pressure (mm Hg)	41 ± 10	46 ± 10	.25
Aortic regurgitation grades I and II [n (%)]	75 (77)	38 (76)	.86
Transfemoral approach [n (%)]	48 (50)	27 (54)	.73

* *P* for comparison between baseline LVEF ≥50% and that of <50%.
† Frailty was assessed according to the criteria of Fried et al.[15]
‡ Renal dysfunction is defined as serum creatinine level >130 μmol/L.

Of the total population, 50 patients (34%) had an LVEF <50% and the remaining patients (n = 97, 66%) had an LVEF ≥50% before TAVI. Patients with an LVEF <50% tended to be in a New York Heart Association functional class of III or higher and to have a higher cardiovascular risk profile (with higher prevalence of diabetes and smoking) as compared with patients with an LVEF ≥50% (Table I).

The AVA was similar in patients with an LVEF <50% and those with that of ≥50%, however, the mean transaortic gradient was lower in patients with impaired LV function (40 ± 15 vs 52 ± 17 mm Hg, $P < .001$). In addition, patients with an LVEF <50% exhibited larger LV volumes, higher LV mass, and larger LA area (Table I).

Intraprocedural outcomes

The procedural success rate was 96% (n = 141) in the population. There were 6 cases of unsuccessful procedure: 4 cases of intraprocedural mortality (3 died from vascular complications, and the fourth patient developed massive aortic regurgitation after prosthesis deployment) and 2 procedures were abandoned (due to risk of ventricular rupture via transapical approach in 1 patient, and because the other patient required emergency surgery after iliac artery perforation).

Finally, there were no significant differences in procedural success, intraprocedural mortality, or MACEs between patients with an LVEF ≥50% and those with that of <50% (Table II). The duration of procedure and amount of contrast used were similar (Table II).

Early clinical outcomes

Total early mortality (≤30 days) was 7% (n = 10) in the entire population, which included 4 (3%) intraprocedural deaths (Table II). The remaining deaths were due to heart failure (n = 3), stroke (n = 1), and noncardiac-related respiratory cause (n = 2).

The difference between patients with an LVEF ≥50% and those with that of <50% in terms of early mortality or each individual adverse event (≤30 days) did not reach statistical significance (Table II). However, the MACE rate was significantly higher in the group with an LVEF <50% when compared with the group with an LVEF ≥50% (20% vs 7%, $P = .029$).

Echocardiographic outcomes

Immediately post-TAVI, significant reduction in the mean transaortic gradient (from 48 ± 17 to 11 ± 5 mm Hg, $P < .05$) and a corresponding increase in the effective AVA were observed in all patients (Table III). These desirable transaortic hemodynamics were maintained at long-term follow-up.

All echocardiographic variables obtained at baseline, immediately post-TAVI, and the latest follow-up in patients with a baseline LVEF ≥50% and those with that of <50% are summarized in Table III. The mean echocardiographic follow-up was 7.2 ± 4.2 months (median = 6.3 months). In both groups, LVEDV index did not change significantly post-TAVI. In contrast, LVESV index decreased significantly from 47 ± 23 mL/m^2 at baseline to 45 ± 20 mL/m^2 and then to 40 ± 20 mL/m^2 (ANOVA $P = .004$) in patients with a baseline LVEF <50%, whereas no significant changes in LVESV index were observed in patients with a baseline LVEF ≥50%. Accordingly, LVEF increased significantly from 37% ± 8% to 46% ± 11% post-TAVI and to 51% ± 11% (ANOVA $P < .001$) at follow-up in patients with a baseline LVEF <50%. In the group with a baseline LVEF ≥50%, however, LVEF remained within normal limits over time. Impor-

Table II. Comparison of intraprocedural and early clinical outcomes for patients with a baseline LVEF ≥50% and those with that of <50%

	All (N = 147)	LVEF ≥50% (n = 97)	LVEF <50% (n = 50)	*P* value*
Intraprocedural				
Procedural success [n (%)]	141 (96)	94 (97)	47 (94)	.41
Mortality [n (%)]	4 (3)	2 (2)	2 (4)	.61
Vascular complication [n (%)]	10 (7)	5 (5)	5 (10)	.31
Fatal [n (%)]	3 (2)	1 (1)	2 (4)	.27
Nonfatal [n (%)]	7 (5)	4 (4)	3 (6)	.69
Cardiac tamponade [n (%)]	4 (3)	4 (4)	0	.30
Acute myocardial infarction [n (%)]	2 (1)	1 (1)	1 (2)	.57
Severe aortic regurgitation [n (%)]	2 (1)	2 (2)	0	.43
Fluoroscopy time (min)†	10 (6-13)	10 (7-13)	10 (5-12)	.54
Procedure duration (min)†	95 (71-115)	95 (78-119)	87 (65-110)	.30
Contrast load (mL)†	150 (120-200)	150 (125-200)	140 (100-200)	.29
In-hospital				
Cardiovascular events [n (%)]	16 (11)	10 (10)	6 (12)	.78
Heart failure [n (%)]	5 (3)	2 (2)	3 (6)	.34
Fatal [n (%)]	3 (2)	2 (2)	1 (2)	1.00
Nonfatal [n (%)]	2 (1)	0	2 (4)	.11
Stroke [n (%)]	4 (3)	1 (1)	3 (6)	.11
Fatal [n (%)]	1 (1)	0	1 (2)	.79
Nonfatal [n (%)]	3 (2)	1 (1)	2 (4)	.27
Heart conduction block requiring pacemaker [n (%)]	7 (5)	6 (6)	1 (2)	.42
Infection [n (%)]	2 (1)	0	2 (4)	.11
Early (≤30 days)				
Total mortality [n (%)]	10 (7)	5 (5)	5 (10)	.31
Combined death, stroke, heart failure, or acute myocardial infarction [n (%)]	17 (12)	7 (7)	10 (20)	.029

* *P* for comparison between baseline LVEF ≥50% and that of <50%.
† Data are presented as median (interquartile range).

Table III. Comparison of echocardiographic parameters at baseline, immediately after the procedure, and latest follow-up

	Baseline	Immediately post-TAVI	Latest follow-up	ANOVA *P* within group
Effective AVA (cm^2)				
LVEF ≥50%	0.66 ± 0.16	2.09 ± 0.42*	2.12 ± 0.58†	<.001
LVEF <50%	0.68 ± 0.17	2.08 ± 0.49*	2.00 ± 0.53†	<.001
Mean gradient (mm Hg)				
LVEF ≥50%	52 ± 17	11 ± 5*	11 ± 9†	<.001
LVEF <50%	40 ± 15	10 ± 4*	10 ± 4†	<.001
LVEDV index (mL/m^2)				
LVEF ≥50%	56 ± 23	55 ± 20	55 ± 21	>.99
LVEF <50%	79 ± 27	79 ± 24	78 ± 23	>.99
LVESV index (mL/m^2)				
LVEF ≥50%	25 ± 18	24 ± 17	23 ± 16	.89
LVEF <50%	47 ± 23	45 ± 20	40 ± 20†	.004
LVEF (%)				
LVEF ≥50%	61 ± 7	59 ± 11	60 ± 11	>.99
LVEF <50%	37 ± 8	46 ± 11*	51 ± 11†‡	<.001
LV mass index (g/m^2)				
LVEF ≥50%	149 ± 40	144 ± 36	130 ± 38†‡	.004
LVEF <50%	174 ± 59	172 ± 52	143 ± 37†‡	<.001
Mitral E/A ratio				
LVEF ≥50%	0.96 ± 0.73	1.10 ± 0.89	0.87 ± 0.50‡	.032
LVEF <50%	1.27 ± 0.95	1.30 ± 0.87	0.93 ± 0.61	.24
Mitral deceleration time (ms)				
LVEF ≥50%	243 ± 80	232 ± 83	251 ± 90	.56
LVEF <50%	223 ± 93	204 ± 68	205 ± 115	.61
LA area (cm^2)				
LVEF ≥50%	23.7 ± 5.7	24.3 ± 6.4	23.0 ± 6.2	.068
LVEF <50%	27.2 ± 6.6	27.4 ± 5.7	25.5 ± 6.2†	.028
Pulmonary artery systolic pressure (mm Hg)				
LVEF ≥50%	41 ± 10	39 ± 11	38 ± 12	.11
LVEF <50%	46 ± 10	43 ± 9	39 ± 11†	.012

* *P* < .05 between baseline and immediately post-TAVI.
† *P* < .05 between baseline and latest follow-up.
‡ *P* < .05 between immediately post-TAVI and latest follow-up.

tantly, all patients showed a significant reduction in LV mass index, regardless of the baseline LVEF (Table III).

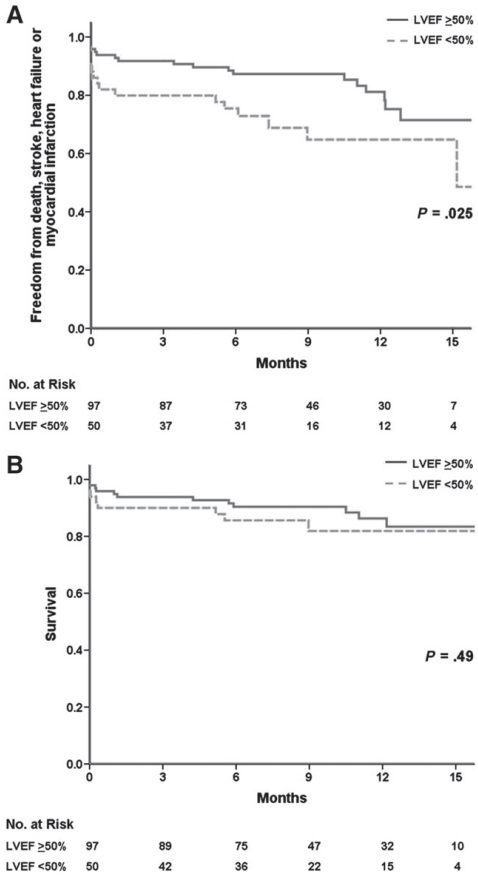
In addition, patients with a baseline LVEF <50% showed significant improvement in LV diastolic function, with a reduction in both LA area and pulmonary artery systolic pressure (Table III). Similarly, patients with a normal baseline LVEF showed a trend toward a decrease in LA area (23.7 ± 5.7 vs 23.0 ± 6.2 cm^2, *P* = .068).

Long-term clinical outcomes

During the follow-up period, there were 12 more cases of death in the total population: 4 cases of cardiovascular death (myocardial infarction, stroke, and infective endocarditis) and 8 cases of noncardiovascular death (gastrointestinal, renal, pulmonary, and orthopedic causes). In addition, further MACEs occurred in 9 patients. Noncardiovascular events (pulmonary diseases) were observed in 2 other patients.

In the Kaplan-Meier analyses of clinical outcomes, the percentage of patients free of MACEs at 6 months and that at 1 year were lower in patients with a baseline LVEF <50% (76% and 65%, respectively) as compared with patients with a baseline LVEF ≥50% (87% and 81%, respectively; log-rank *P* = .025; Figure 1, *A*). In addition, the univariate Cox proportional hazards analysis identified 5 potential baseline predictors of cumulative MACEs: logistic EuroSCORE (hazard ratio [HR] = 1.02, 95% confidence interval [CI] = 1.00-1.05, *P* = .10), presence of frailty (HR = 3.14, 95% CI = 1.59-6.20, *P* = .001), peripheral vascular disease (HR = 1.73, 95% CI = 0.88-3.38, *P* = .11), history of previous coronary artery bypass (HR = 1.75, 95% CI = 0.88-3.47, *P* = .11), and baseline LVEF (HR = 0.98, 95% CI = 0.96-1.00, *P* = .063). In the

Figure 1



A, Kaplan-Meier curves of freedom from death, nonfatal stroke, heart failure, or nonfatal myocardial infarction for patients who underwent TAVI with a baseline LVEF ≥50% and those with that of <50%. **B**, Kaplan-Meier curves of survival for patients who underwent TAVI with a baseline LVEF ≥50% and those with that of <50%.

final multivariate model, presence of frailty (HR = 4.20, 95% CI = 2.00-8.84, $P < .001$) and baseline LVEF (HR = 0.97, 95% CI = 0.94-0.99, $P = .017$) emerged as the only independent predictors of cumulative MACEs.

Nonetheless, the general survival rates at 1, 6, and 12 months in patients with a baseline LVEF ≥50% and those with that of <50% were not significantly different, as illustrated in Figure 1, *B* (95%, 90%, and 86% vs 90%, 86%, and 82%, respectively; log-rank $P = .49$).

TAVI versus surgery

Ninety-nine patients who underwent SAVR at the Leiden University Medical Center were retrospectively recruited from the surgical database and divided into 2 subgroups based on an LVEF <50% (n = 30) or that of ≥50% (n = 69) before surgery to evaluate whether the clinical outcome of TAVI is similar to that of the surgical approach. Table IV summarizes the baseline characteristics of patients who underwent SAVR. These control patients were frequency matched to the studied population in terms of age (79.3 ± 5.6 vs 80.5 ± 6.3 years, $P = .23$), male gender (34.8% vs 36.1%, $P = .86$), and AVA (0.71 ± 0.14 vs 0.66 ± 0.16 cm^2, $P = .06$) for the group with a baseline LVEF ≥50%. In patients with a baseline LVEF <50%, similar matching was performed with regard to their age (77.3 ± 5.0 vs 79.8 ± 7.5 years, $P = .08$), male gender (73.3% vs 56.0%, $P = .12$), and AVA (0.73 ± 0.24 vs 0.68 ± 0.17 cm^2, $P = .37$). Figure 2 demonstrates that survival of patients who underwent TAVI compared favorably with that of patients who underwent SAVR (log-rank $P = .40$), regardless of LV function at baseline.

Discussion

The Euro Heart Survey indicated that apart from advanced age, LV systolic dysfunction is the other major reason to deny surgery in patients with severe AS.[10] In fact, the outcome of SAVR is highly dependent on preoperative LV function.[4,7,24] Recently, TAVI has been introduced as a therapeutic alternative in patients with excessive operative risk. However, little is known on the impact of preoperative LV function on clinical and echocardiographic outcomes post-TAVI.

The present study demonstrates that TAVI is a feasible and effective therapeutic option for high-risk patients with severe AS, irrespective of baseline LVEF. Significant improvements in transvalvular hemodynamics and in LV performance were observed post-TAVI. In particular, patients with an LVEF <50% showed LV reverse remodeling, with marked improvements of LV systolic function and diastolic function.

In addition, early and late all-cause mortality rates were not significantly different between patients with normal and those with impaired LV function, despite a higher rate of combined MACEs in patients with a baseline LVEF <50%. Predictors of cumulative MACEs were the presence of frailty and baseline LVEF. Importantly, the long-term survival curves of patients with normal and those with impaired LV function who underwent TAVI were comparable with those of patients who underwent SAVR (the standard therapy for severe symptomatic AS[2]).

Early clinical outcomes

In the current study, the procedural success rate for TAVI was 96%, in line with results of a recent series that reported improved procedural success rates of 91%-

Table IV. Baseline clinical and echocardiographic characteristics of patients who underwent SAVR with a baseline LVEF ≥50% and those with that of <50%

	LVEF ≥50% (n = 69)	LVEF <50% (n = 30)
Age (y)	79.3 ± 5.6	77.3 ± 5.0
Male [n (%)]	24 (35)	22 (73)
Logistic EuroSCORE (%)	9.6 ± 5.1	17.8 ± 13.0
New York Heart Association functional class of III or higher [n (%)]	30 (44)	14 (47)
Previous myocardial infarction [n (%)]	10 (15)	11 (37)
Previous coronary bypass surgery [n (%)]	8 (11)	7 (23)
Hypertension [n (%)]	35 (51)	11 (37)
Hypercholesterolemia [n (%)]	17 (25)	9 (30)
Diabetes [n (%)]	15 (22)	8 (27)
Smoking [n (%)]	14 (20)	6 (20)
Renal dysfunction [n (%)]*	4 (6)	6 (20)
Hemoglobin (g/dL)	12.6 ± 1.9	13.3 ± 2.0
Echocardiography		
AVA (cm^2)	0.71 ± 0.14	0.73 ± 0.24
Mean aortic gradient (mm Hg)	49 ± 18	33 ± 16
LVEF (%)	60 ± 6	35 ± 8
Concomitant coronary bypass surgery [n (%)]	29 (42)	15 (50)

* Renal dysfunction is defined as serum creatinine level >130 μmol/L.

94%.[12,14] Despite their higher risk profile, patients with a baseline LVEF <50% showed similar success rate (97% vs 94%) and perioperative adverse events relative to patients with a baseline LVEF ≥50% (Table II). Of note, procedure-specific variables, such as procedure duration and total contrast volume, were also similar. Therefore, the present study highlights the feasibility of TAVI in a multicenter setting and regardless of baseline LV function.

The overall early 30-day mortality was 7%, which compares favorably with the recently published multicenter Canadian experience of 10%.[14] Although no significant differences in terms of 30-day mortality were observed between patients with preserved and those with impaired LV function (10% vs 5%, $P = .31$), patients with an LVEF <50% had a more than 2-fold increase in the risk of combined MACEs (20% vs 7%, $P = .03$) as compared with patients with an LVEF ≥50%. Therefore, in patients undergoing TAVI, the presence of LV dysfunction has an additional negative impact on early morbidity with an increased incidence of combined MACEs without affecting the early all-cause mortality significantly.

Echocardiographic outcomes

As a result of chronic LV pressure overload associated with severe AS, the LV wall thickens initially in an attempt to limit wall stress and to maintain adequate systolic function.[16] However, when the wall stress exceeds LV compensatory capacity, LV systolic dysfunction ensues from the effect of afterload mismatch.[3] Consequently, in the absence of significant primary myocardial dysfunction, valve replacement (TAVI or SAVR) results in improvement of LV function.[16] Accordingly, marked LV reverse remodeling and improvement in LV systolic function were observed especially in patients with a baseline LVEF <50%, in whom the mean LVEF increased over time. Thus, the present study confirms that LV dysfunction, when it is due to afterload mismatch associated with severe AS, may be reversible following TAVI.

Significant improvement in other echocardiographic parameters was also observed. LV mass regression occurred in all patients due to the marked improvement in LV hemodynamics post-TAVI. Similarly, as a result of the reduction in LV filling pressure, significant improvement in LV diastolic function was observed (a reduction in LA area and pulmonary artery systolic pressure) (Table III). Of note, this improvement was more marked in patients with a baseline LVEF <50%, who also showed a larger LA area at baseline. LA dilatation has been recognized as a marker of disease progression in patients with AS, reflecting the increase in LV filling pressures associated with severe AS.[25] This study highlights that LA enlargement could also be attenuated post-TAVI.

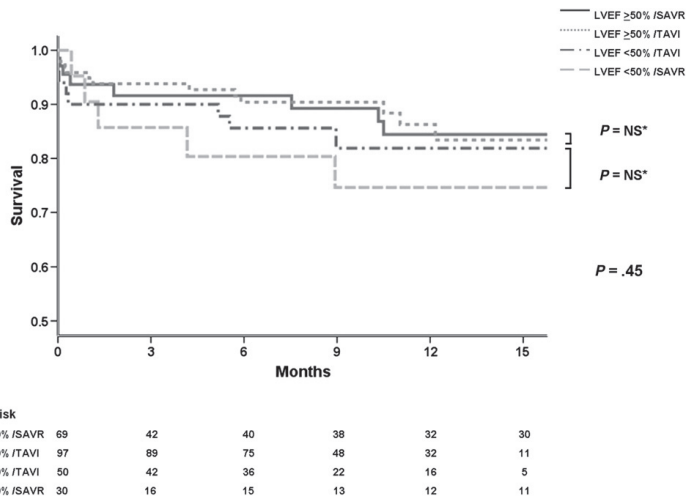
Long-term clinical outcomes

This study shows that during long-term follow-up post-TAVI, patients with a baseline LVEF <50% were associated with higher incidence of combined MACEs as compared with those with a normal LVEF (Figure 1, *A*). Moreover, other than baseline LVEF, the physical performance status of patients (expressed by frailty in the present study) was an independent predictor of MACE-free survival. Similarly, preprocedural functional status, as expressed using a different scoring index (Karnofsky index),[26] has been shown to be able to predict outcome post-TAVI in a recent study of 168 patients who underwent self-expanding prosthesis implantation.[27] These findings suggest that incorporating the functional assessment of high-risk patients with AS in the selection criteria for TAVI may be more appropriate than the currently used scoring systems to identify those patients who will derive maximum benefit from this new intervention.

In terms of all-cause mortality, the cumulative survival rates were similar in both groups (Figure 1, *B*). A possible explanation for this finding is that most deaths occurring after 30 days were not from cardiovascular causes but were related to advanced age and the presence of comorbidities. In the series of Webb et al,[12] who followed up on 168 patients post-TAVI, late mortality was also primarily determined by underlying comorbidities.

Furthermore, in the present study, patients who underwent TAVI had survival curves similar to those of patients who underwent SAVR (Figure 2). In particular, no significant differences were observed in survival rates at 6 months (92% vs 90%) and 1 year (84% vs 86%, log-rank

Figure 2



Kaplan-Meier curves of survival for patients with a baseline LVEF ≥50% and those with that of <50% who underwent SAVR or TAVI. The asterisk indicates comparison between SAVR and TAVI.

P = .82) between patients with a baseline LVEF ≥50% who underwent SAVR and those who underwent TAVI. Similarly, the type of procedure (SAVR or TAVI) did not have an impact on the survival rates at 6 months (80% vs 86%) or 1 year (75% vs 82%, log-rank *P* = .99) in patients with a baseline LVEF <50%. Therefore, the present study suggests that in patients at high operative risk, in whom SAVR would be excluded due to advanced age or depressed LVEF or a combination of factors, TAVI should be strongly considered. In fact, these patients, if left on medical therapy, would have high morbidity and mortality rates. Varadarajan et al[6] studied a cohort of 277 elderly patients (mean LVEF = 52% ± 20%) and showed that patients with symptomatic severe AS and left unoperated have significantly worse prognosis than those undergoing SAVR (52% vs 87% survival rate at 1 year). Moreover, previous studies[5,6,8] have indicated that the presence of LV dysfunction has further negative impact on the survival of patients with severe AS. Tarantini et al[8] reported that in patients with severe AS and depressed LVEF, the mortality rate was very high, with only 16% of patients alive at 2 years. Therefore, the current study suggests that TAVI may improve the survival of high-risk patients with severe AS to a level that is possibly comparable with that of SAVR (the standard therapy for symptomatic severe AS[2]), regardless of baseline LV function.

Limitations

Although the data were prospectively collected, all adverse events were collected from the electronic database of each center. Nonetheless, the investigators endeavored to ensure accuracy of the information provided. In addition, we acknowledge the limitations in comparing TAVI versus SAVR (using a control cohort) and in particular the presence of potential confounding factors despite the matching criteria. For example, due to a selection bias associated with TAVI (after SAVR was denied), patients who underwent TAVI carry significantly higher operative risk compared with those who underwent SAVR. Nonetheless, this inherent difference would have biased the results toward a larger difference in outcomes, favoring those of surgery. On the contrary, the present study shows that patients who underwent TAVI had comparable long-term survival outcome as those who underwent SAVR. The present study may shed some light on the difference in outcomes between these 2 approaches before the results of a randomized controlled trial become available.

Conclusions

The present study shows that the patients with severe AS at high operative risk benefited from TAVI in terms of improvement in LV function and survival, regardless of

baseline LVEF. Although patients with an LVEF <50% were at higher risk of combined MACEs when compared with patients with an LVEF ≥50%, the early and long-term all-cause mortality rates were similar. Importantly, TAVI resulted in a long-term survival that was comparable with that of a matched group of patients who underwent SAVR (the current standard of care for severe AS[2]).

Disclosures

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11

Outcomes after transcatheter aortic valve implantation: transfemoral versus transapical approach

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Outcomes After Transcatheter Aortic Valve Implantation: Transfemoral Versus Transapical Approach

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Background. **Transcatheter aortic valve implantation is commonly implanted through a transfemoral (TFA) or transapical approach (TAA) for patients with severe aortic stenosis. This study aimed to describe the clinical and echocardiographic outcomes of TFA versus TAA.**

Methods. **Clinical and echocardiographic evaluations were performed at baseline, post-TAVI (transcatheter aortic valve implantation), at 6 and 12 months follow-up in 107 consecutive patients who underwent TAVI with balloon-expandable valves.**

Results. **The TFA was performed in 44% and the remaining patients underwent TAA. Although procedural complications were not significantly different in both approaches, more vascular complications were observed in the TFA group (18% vs 5%, $p = 0.053$). Patients with TAA required shorter fluoroscopy time (median 5 vs 12 min, $p < 0.001$), less contrast volume (median 80 vs 173 mL, $p < 0.001$), and similar length of hospitalization, as compared with TFA. Importantly, the early 30-day mortality (TFA: 11.1% vs TAA: 8.5%, $p = 0.74$) were not significantly different between the 2 approaches. Midterm survival at 6 months and 1 year was comparable between TFA and TAA (6 months: 88.9% vs 85.7% and 1 year: 80.2% vs 85.7%). All patients achieved immediate and sustained improvements in transvalvular hemodynamics, together with significant left ventricular mass regression (137 ± 39 vs 113 ± 30 g/m^2, $p < 001$) and left atrial volume reduction (48 ± 17 vs 34 ± 14 mL/m^2, $p < 0.001$) at 6 months or less.**

Conclusions. **Early, midterm, clinical, and echocardiographic outcomes were comparable in both approaches. However, TAA has the additional benefit of reducing radiation exposure and contrast use intraoperatively without prolonging the length of hospital stay.**

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Transcatheter aortic valve implantation (TAVI) is a feasible therapeutic alternative for patients with symptomatic severe aortic stenosis (AS) and high operative risk [1–3]. In addition, TAVI has been shown to improve both the symptoms and clinical outcomes of these patients [3, 4]. Currently, the balloon-expandable Edwards SAPIEN bioprosthetic valve (Edwards Lifesciences Inc, Irvine, CA) can be implanted through a transfemoral (TFA) or a transapical approach (TAA). Although the TFA is the preferred approach for its less invasive nature, this option is not feasible in patients with unfavorable anatomy of the peripheral arteries and aorta, and with subsequent risk of major vascular complications [5]. Accordingly, the TAA, which involves a minithoracotomy, has been explored with promising results [1–3, 6]. However, there are limited studies comparing the immediate, short-term, and midterm clinical results of both approaches, TFA versus TAA.

Furthermore, favorable left ventricular (LV) remodeling and function postsurgical aortic valve replacement for AS have been documented [7] but little is known about the changes in valvular hemodynamics and its

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consequence on LV function after TAVI. The present study describes the early and midterm clinical outcomes of the 2 approaches (TFA vs TAA) and evaluates the changes in LV performance immediately postprocedure and at midterm ($\geq$ 6 months) follow-up.

Patients and Methods

Over a period of 2.5 years, a total of 107 consecutive patients with severe symptomatic AS and high surgical risk or contraindications for surgical aortic valve replacement were referred for TAVI at the Leiden University Medical Center. The patients were evaluated by a multidisciplinary team including cardiothoracic surgeons and interventional cardiologists. The preprocedural evaluation consisted of clinical evaluation, transthoracic echocardiography, coronary angiography, and angiography of the aorto-ilio-femoral system. Clinical evaluation included the assessment of operative risk according to the logistic European system for cardiac operative risk evaluation [8] and the Society of Thoracic Surgeons score, evaluation of comorbidities, previous thoracic surgery, or radiation and physical frailty [9]. This evaluation was conducted according to the clinical protocol of the institution. All patients provided informed consent for the procedures. Clinical and echocardiographic data were prospectively collected in electronic patient dossier (EPD vision version 8.3.3.6; Leiden, The Netherlands) and retrospectively analyzed with approval of the Institutional Review Board.

All patients underwent transthoracic echocardiography at baseline, postprocedure, and at 6 and 12 months follow-up. The LV end-diastolic and end-systolic volumes were measured, indexed to body surface area, and the LV ejection fraction was derived from the biplane Simpson method [10]. Standard LV dimensions and mass were measured [10, 11]. Peak and mean transaortic pressure gradients were calculated and aortic valve area was determined by the continuity equation [12]. Severe AS was defined as a mean pressure gradient of 40 to 50 mm Hg or greater, or a valve area less than 1 cm^2 [13, 14]. Aortic regurgitation (AR) was assessed using color Doppler and its severity was assessed according to current guidelines [13–15]. In addition, diastolic function was assessed by the ratio of the transmitral early filling velocity (E-wave) to the late diastolic filling velocity (A-wave) and deceleration time of the E-wave. Pulmonary artery systolic pressure was also calculated from the peak velocity of the tricuspid regurgitation jet [16]. Finally, maximal left atrial volumes were measured using the biplane Simpson method and indexed to body surface area [10].

All procedures were performed at the catheterization laboratory under general anesthesia with transesophageal echocardiography and fluoroscopy guidance. The Edwards SAPIEN valves (Edwards Lifesciences Inc) of either 23 mm or 26 mm were used. The retrograde TFA was considered first option whereas the TAA was recommended if any of the following criteria were present: previous peripheral vascular surgery or aortoiliac intervention; significant peripheral artery disease; iliofemoral arteries less than 7 to 8 mm (for 23 or 26 mm valve, respectively); marked tortuosity of the aorto-ilio-femoral system; or abdominal aortic aneurysm and porcelain aorta [2, 5].

As previously described, the implantation of the valve was preceded by balloon dilatation of the native aortic valve and rapid pacing was required during valve deployment [3]. For the TFA, transarterial access was gained after surgical cut-down, whereas an anterior minithoracotomy followed by direct needle puncture of the LV apex was performed for the TAA [3]. At the end of procedure, all the access sites were closed surgically. Procedural success was defined as successful implantation of a functioning aortic prosthesis without intraprocedural mortality [2, 3]. Total iodinated contrast volume consumed, duration of fluoroscopy, and the procedure were recorded. Procedural duration was measured from the time of skin incision or arterial puncture to the closure of the access site.

Systematic clinical evaluations were obtained post-TAVI, before hospital discharge, and at 6 and 12 months. Intraprocedural mortality included any death that occurred before extubation in the catheterization laboratory. In-hospital events included all-cause mortality, stroke, atrioventricular conduction block requiring pacemaker, bleeding, infection, and heart failure decompensation. Bleeding was defined as any significant blood loss requiring surgical intervention, blood transfusion, or both. Infection was defined as any utilization of intravenous antibiotics for clinically identifiable source or elevated inflammatory markers. In addition, septicemia, valvular endocarditis, and wound infection were recorded as major infection events. Total early mortality included both intraprocedural, in-hospital deaths, and all deaths within the first 30 days. Midterm outcome measures included all major adverse cardiac, cerebrovascular, valve related, or noncardiac events requiring hospitalization.

Statistical Analysis

Continuous variables were presented as mean ($\pm$SD) or median (interquartile ranges) and categoric variables as frequencies (percentages), as appropriate. Clinical and echocardiographic characteristics of the patients were compared based on the approach of TAVI (TFA vs TAA). Continuous variables were compared using the unpaired Student *t* test or Mann-Whitney *U* test, and for categoric variables the χ^2 test or Fisher exact test, as appropriate. Repeated measures analysis of variance (ANOVA) was used to analyze the repeated continuous data and post hoc analysis for significant results were performed using the Bonferroni correction. Survival was evaluated using the Kaplan-Meier analysis and the log-rank test was used to measure the differences between groups. A p value less than 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS for Windows, version 16 (SPSS Inc, Chicago, IL).

Results

A total of 107 patients underwent TAVI after multidisciplinary screening. Three cases (2.8%) were abandoned during the procedure due to the risk of coronary occlu-

sion from heavily calcified valve leaflets or ventricular rupture from friable myocardium by the TAA. Two patients subsequently received balloon valvuloplasty and were alive at last follow-up. The third patient, who did not receive balloon valvuloplasty due to the risk of worsening of baseline AR, died from heart failure 8 months later. The final analysis included only patients who received TAVI (n = 104). Table 1 shows the baseline clinical characteristics. Fifty-nine patients (56.7%) underwent TAA due to unsuitable arterial anatomy for TFA. Accordingly, there were more patients with significant peripheral vascular disease in the TAA group (67.8% vs 11.1%, $p < 0.001$). Patients with peripheral arterial disease, but had adequate ilio-femoral anatomy, proceeded with the TFA [2, 5].

Procedural success rate was 92.5% and the intraprocedural mortality rate was 4.8%. The duration of fluoroscopy (median 12 vs 5 minutes, $p < 0.001$), total contrast volume use (median 173 vs 80 mL, $p < 0.001$), and procedural duration (median 71 vs 64 minutes, $p = 0.008$) were significantly more in the TFA than the TAA group. Five (4.8%) intraprocedural deaths were the following: 3 fatal vascular complications through the TFA with perforation of iliac arteries (n = 2) and rupture of the descending aorta (n = 1), and 2 deaths during TAA (severe AR after prosthesis deployment and cardiogenic shock). Attempts to seal off the iliac artery perforation with covered stents were unsuccessful in the first 2 cases, leading to death despite emergency laparotomy. The remaining patients died before bailout procedures such as emergency valve-in-valve or endovascular aortic repair could be attempted. There was a strong trend toward more vascular complications in the TFA group (17.8% vs 5.1%, $p = 0.053$). All 3 cases of cardiac tamponade were successfully drained.

A comparison of in-hospital outcomes between the 2 approaches is summarized in Table 2. The total 30-day mortality was 9.6%. There were 4 cases of in-hospital mortality: heart failure (n = 3) and stroke (n = 1). One additional death occurred on day 22 (massive bleeding peptic ulcer) after the first hospitalization. Length of hospitalization was similar in both approaches (median 6 days for both, $p = 0.21$).

Median follow-up duration was 12.2 (interquartile range 5.6 to 22.1) months. Late complications were uncommon after 30 days. Six deaths occurred between 30 days and 1 year: 3 cardiovascular deaths (endocarditis, myocardial infarction and stroke) and the remaining cases were noncardiac related

Table 1. Baseline Clinical Characteristics of the Study Population and Comparison Between 2 Approaches, Transapical Versus Transfemoral

Variable	All (n = 104)	Transfemoral (n = 45)	Transapical (n = 59)	*p* Value
Age (years)	80.6 ± 7.9	82.2 ± 7.1	79.4 ± 8.3	0.072
Male	50.0%	46.7%	52.5%	0.69
Body surface area (m^2)	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.82
Logistic EuroSCORE (%)	21.3 ± 11.8	20.1 ± 11.7	22.6 ± 11.9	0.20
STS score (%)	8.7 ± 3.6	8.5 ± 3.8	8.9 ± 3.5	0.61
New York Heart Association functional class ≥ III	68.3%	64.4%	71.2%	0.53
Heart rhythm				
Sinus rhythm	72.1%	77.8%	67.8%	0.28
Atrial fibrillation	21.2%	17.8%	23.7%	0.63
Pacemaker	6.7%	4.4%	8.5%	0.70
Renal dysfunction[a]	22.1%	22.2%	22.0%	1.00
Hemoglobin (g/dL)	12.2 ± 1.6	12.0 ± 1.6	12.3 ± 1.5	0.36
Previous myocardial infarction	23.1%	22.2%	23.7%	1.00
Previous coronary bypass surgery	40.0%	33.3%	42.4%	0.42
Peripheral vascular disease	43.3%	11.1%	67.8%	<0.001
Previous aortofemoral bypass or stenting	3.8%	0%	6.8%	0.13
Abdominal aortic aneurysm	2.9%	0%	5.1%	0.26
Porcelain aorta	3.8%	0%	6.8%	0.13
Hypertension	59.6%	51.1%	66.1%	0.16
Hypercholesterolemia	44.2%	33.3%	52.5%	0.073
Diabetes	27.9%	28.9%	27.1%	1.00
Chronic obstructive pulmonary disease	26.9%	24.4%	28.8%	0.16
Previous stroke	11.5%	4.4%	17.0%	0.064
Frailty	36.5%	28.9%	42.4%	0.12
Smoking	35.6%	26.7%	42.4%	0.11

[a] Renal dysfunction was defined as serum creatinine exceeding 130 μmol/L.

EuroSCORE = European system for cardiac operative risk evaluation; STS = The Society of Thoracic Surgeons.

Table 2. Comparison of Outcomes Within Index Hospitalization for Transfemoral and Transapical Approaches

Variable	All (n = 104)	Transfemoral (n = 45)	Transapical (n = 59)	*p* Value
Intraprocedural:				
Mortality	4.8%	6.7%	3.4%	0.65
Vascular complication	10.6%	17.8%	5.1%	0.053
Fatal	2.9%	6.7%	0%	0.078
Non-fatal	7.7%	11.1%	5.1%	0.29
Cardiac tamponade	3.8%	2.2%	5.1%	0.63
Fluoroscopy time (minutes)[a]	8 (5–12)	12 (10–15)	5 (4–8)	<0.001
Procedure duration (minutes)[a]	68 (53–85)	71 (58–98)	64 (49–80)	0.008
Contrast load (mL)[a]	100 (75–170)	173 (118–200)	80 (70–109)	<0.001
In-hospital:				
Mortality	3.8%	4.4%	3.4%	1.00
Heart failure	2.9%	4.4%	1.7%	0.58
Fatal stroke	1.0%	0%	1.7%	1.00
Stroke	3.8%	4.4%	3.4%	1.00
Non-fatal	2.9%	4.4%	1.7%	0.58
AV conduction block requiring pacemaker	3.8%	4.4%	3.4%	1.00
Bleeding	11.5%	6.7%	15.3%	0.22
Major infection	0%	0%	0%	1.00
Minor infection	8.7%	4.4%	11.9%	0.29
Hospital stay, days[a]	6 (5–8)	6 (5–7)	6 (5–8)	0.21
Early (<30 days)				
Total mortality	9.6%	11.1%	8.5%	0.74

[a] Data are presented as median (interquartile range).

AV= atrioventricular.

(bleeding peptic ulcer and end-stage lung disease). Overall survival at 1, 6, and 12 months was 90.4%, 87.2%, and 83.0%, respectively. Figure 1 shows no significant difference between the 2 approaches in terms of survival (log-rank, $p = 0.63$). Significant improvement in New York Heart Association functional class was noted post-TAVI (from 2.8 ± 0.8 to 1.5 ± 0.6 at 6 months, $p < 0.001$), which was maintained at 1 year. No difference in functional class was observed between the 2 approaches (Fig 2).

All echocardiographic data obtained at baseline, post-procedure, and at 6 months or greater were compared (Table 3). Significant increase in aortic valve area was

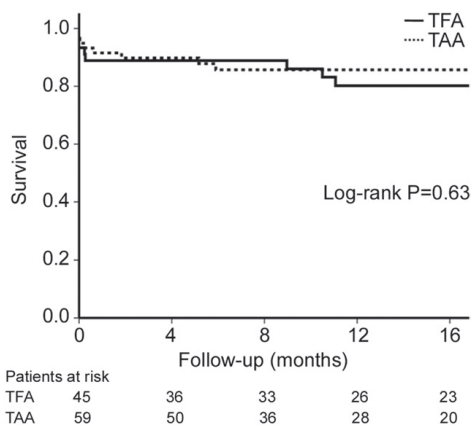

Fig 1. Kaplan-Meier curves of survival after transcathether aortic valve implantation by the two approaches, transapical (TAA) versus transfemoral (TFA).

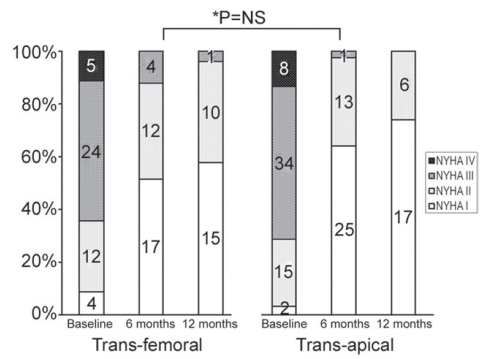

*Fig 2. Follow-up of New York Heart Association (NYHA) functional class at 6 and 12 months in the 2 approaches (transapical versus transfemoral). (*Comparison between 2 approaches. Absolute numbers are shown inside the bars; NS = not significant.)*

Table 3. Comparison of Echocardiographic Parameters at Baseline, Postprocedure, and at Latest Follow-Up Echocardiography

Variable	Baseline (n = 104)	Postprocedure (n = 97)	Latest Follow-Up (≥ 6 months) (n = 71)	ANOVA *p* Value
Aortic valve area (cm^2)				
All patients	0.7 ± 0.2	2.0 ± 0.4[a]	1.9 ± 0.4[b]	<0.001
Transfemoral	0.7 ± 0.2	2.0 ± 0.5[a]	1.8 ± 0.4[b]	<0.001
Transapical	0.8 ± 0.2	2.0 ± 0.3[a]	1.9 ± 0.3[b]	<0.001
Mean transaortic gradient (mm Hg)				
All patients	41 ± 16	8 ± 3[a]	9 ± 6[b]	<0.001
Transfemoral	43 ± 19	8 ± 3[a]	10 ± 7[b]	<0.001
Transapical	39 ± 12	8 ± 3[a]	8 ± 4[b]	<0.001
Left ventricular end-diastolic volume index (mL/m^2)				
All patients	69 ± 28	68 ± 25	71 ± 27	0.31
Transfemoral	63 ± 26	64 ± 25	65 ± 24	0.70
Transapical	76 ± 29	73 ± 25	78 ± 30	0.30
Left ventricular end-systolic volume index (mL/m^2)				
All patients	36 ± 25	33 ± 22	36 ± 23	0.18
Transfemoral	32 ± 24	29 ± 21	31 ± 21	0.25
Transapical	40 ± 25	38 ± 22	41 ± 24	0.43
Left ventricular ejection fraction (%)				
All patients	53 ± 14	55 ± 13	52 ± 13	0.16
Transfemoral	55 ± 14	59 ± 13	55 ± 15	0.07
Transapical	52 ± 14	50 ± 13	50 ± 12	0.48
Left ventricular septal wall thickness (mm)				
All patients	13 ± 3	13 ± 3	11 ± 2[b,c]	<0.001
Transfemoral	12 ± 3	12 ± 2	10 ± 1[b,c]	<0.001
Trans-apical	12 ± 2	12 ± 2	11 ± 2[b,c]	<0.001
LV posterior wall thickness (mm)				
All patients	12 ± 2	12 ± 2	11 ± 2[b,c]	<0.001
Transfemoral	13 ± 3	12 ± 2	11 ± 2[b,c]	<0.001
Transapical	12 ± 2	12 ± 2	11 ± 2[b,c]	0.003
Left ventricular mass index (g/m^2)				
All patients	137 ± 39	132 ± 37	113 ± 30[b,c]	<0.001
Transfemoral	130 ± 40	123 ± 31	104 ± 30[b,c]	<0.001
Transapical	143 ± 37	140 ± 40	122 ± 29[b,c]	<0.001
Mitral E/A ratio				
All patients	1.0 ± 0.8	1.4 ± 1.1[a]	0.9 ± 0.7[c]	0.003
Transfemoral	0.9 ± 0.6	1.5 ± 1.4[a]	0.8 ± 0.5[c]	0.010
Transapical	1.1 ± 0.9	1.3 ± 0.8	1.0 ± 0.9	0.15
Mitral E wave deceleration time (ms)				
All patients	233 ± 80	217 ± 81	235 ± 78	0.25
Transfemoral	230 ± 81	214 ± 93	240 ± 69	0.36
Transapical	235 ± 81	219 ± 70	230 ± 86	0.48
Pulmonary artery systolic pressure (mmHg)				
All patients	42 ± 13	41 ± 14	36 ± 14[b,c]	0.005
Transfemoral	41 ± 14	42 ± 16	37 ± 16	0.10
Transapical	43 ± 11	39 ± 11	32 ± 8[b]	0.036
Left atrial volume index (mL/m^2)				
All patients	48 ± 17	45 ± 20	34 ± 14[b,c]	<0.001
Transfemoral	50 ± 20	49 ± 25	32 ± 17[b,c]	<0.001
Transapical	47 ± 14	42 ± 15[a]	36 ± 12[b,c]	<0.001

[a] $p < 0.05$ between baseline and postprocedure. [b] $p < 0.05$ between baseline and latest follow-up echocardiography. [c] $p < 0.05$ between postprocedure and latest follow-up echocardiography.

ANOVA = analysis of variance; E/A ratio = early transmitral flow velocity to atrial flow velocity.

observed in all patients postprocedure and maintained at 6 months or greater (from 0.7 ± 0.2 cm^2 to 2.0 ± 0.4 cm^2, and then to 1.9 ± 0.4 cm^2), regardless of the approach. This was paralleled with similar reduction in mean gradient.

Although there was no significant change in LV volumes and ejection fraction, LV mass index decreased significantly from 137 ± 39 g/m^2 to 132 ± 37 g/m^2, and then to 113 ± 30 g/m^2 in the whole group (ANOVA $p < 0.001$). This LV mass regression remained significant when analyzed according to procedural approach (Table 3). Regarding the analysis of diastolic function, left atrial volume decreased from 48 ± 17 mL/m^2 to 34 ± 14 mL/m^2 at 6 months or greater for the whole population (ANOVA $p < 0.001$), which remained significant in both approaches (Table 3). Mild AR was noted in 57.7% and 50.7% of patients postprocedure and at 6 months or greater, respectively. Conversely, significant AR post-TAVI (of grade > II) was infrequent and was only observed in 5 patients postprocedure (Fig 3). Importantly, no severe AR was observed over time. The TFA or TAA did not affect the outcome of AR post-TAVI.

Comment

The present study demonstrated that TAVI by the TAA or TFA had comparable clinical outcomes and midterm survival in high-risk patients with severe AS. Importantly, the TAA did not prolong hospital stay but reduced fluoroscopy time, amount of contrast used intraprocedurally, and procedural duration. Furthermore, TAVI resulted in favorable and sustained improvements in transvalvular hemodynamics, with regression in LV mass and left atrial volume on midterm follow-up.

The procedural success rate of 92.5% in our initial single-center experience is encouraging and is in line with the 91% to 94% reported in other series [2, 3]. Although the overall early 30-day mortality for this high-risk group is not low (9.6%) in this study, this compares well to the reported 30-day mortality rate of 7.5% to 10.5% for this group of octogenarians (n = 282) undergoing isolated aortic valve surgery [17]. More importantly, the survival rate after TAVI is superior to that observed in patients who did not undergo aortic valve surgery for severe AS. In a recent randomized trial of 358 patients who were not candidates for surgery and assigned to TFA-TAVI or standard therapy including balloon valvuloplasty [18], the survival 1 year was 69.3% with TAVI, compared with only 49.3% with current standard therapy for severe AS.

Currently, the TFA is the initial preferred approach for TAVI in most centers. In this study, 56.7% of patients were not candidates for the TFA due to unsuitable peripheral arterial or aortic anatomy. As such, these patients would be denied a potentially life-saving and symptom-relief procedure if an alternative access such as TAA was not available. This is consistent with the study of Rodes-Cabau and colleagues [19], in which at least 51% of their patients underwent TAA due to unfavorable peripheral anatomy. Accordingly, expertise in both approaches and a multidisciplinary care are vital in providing optimal treatment to this group of high-risk patients with symptomatic AS.

The present study highlighted several important technical differences between the 2 approaches. First, the TAA group was associated with significantly less contrast use. This observation may be clinically important as most of these elderly patients are susceptible to contrast-induced nephropathy by virtue of advanced age and multiple comorbidities. Bagur and colleagues [20] have highlighted that acute kidney injury occurred in 12% of the patients' post-TAVI and its occurrence was associated with at least a fourfold increase in postoperative mortality. Thus, TAA may be a preferred approach in patients with concomitant renal dysfunction and unfavorable vascular access. Second, consistent with the study of Bleiziffer and colleagues [21], we found shorter total fluoroscopy time in patients with TAA than with TFA. A plausible explanation for this is that less time is required for valve implantation by the TAA due to easier manipulation and control of the device with a shorter distance between the aortic valve and the access site. This was reflected in shorter total fluoroscopy time associated with TAA. Finally, we observed similar length of hospital stay in both approaches. Currently, there is limited data comparing the procedural time and hospital stay.

In terms of intraprocedural complications, there was a trend toward a higher prevalence of vascular complications in patients who underwent TFA (Table 2). Similar nonstatistical significant observation was reported by Webb and colleagues [3] in 168 patients, where more vascular injury occurred in patients with TFA than TAA (8% vs 3.6%). The development of smaller-sized delivery system, better patient preprocedural screening and the experience of the operators are vital in improving the immediate outcomes of TAVI, particularly with the TFA

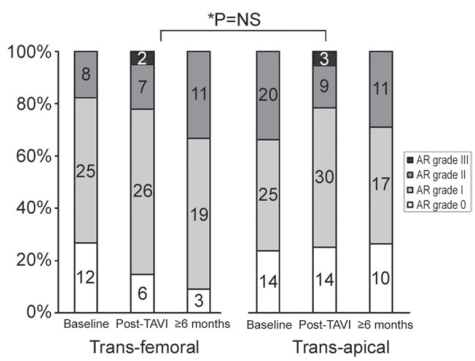

*Fig 3. Comparison of aortic regurgitation severity assessed at baseline, postprocedure, and at latest follow-up echocardiography (≥ 6 months) for transfemoral and transapical approaches. (*Comparison between 2 approaches. Absolute numbers are shown inside the bars; AR = aortic regurgitation; NS = not significant; post-TAVI = post-transcatheter aortic valve implantation.)*

[3, 5, 22]. The present study showed comparable stroke occurrence in the 2 approaches. In contrast, Himbert and colleagues [22] observed 3 stroke events after TFA but none occurred by TAA ($p = 0.23$). Finally, the incidence of permanent pacing after TAVI in our population was low (3.8%), which is consistent with the observation of Webb and colleagues who reported only 5.4% of patients required permanent pacemaker after balloon-expandable valves implantation. Importantly, the present study demonstrated that implantation approach did not affect both the early survival at 30 days and midterm survival at 6 months (TFA: 88.9% vs TAA: 85.7%) and at 12 months (TFA: 80.2% vs TAA: 85.7%, Fig 1).

Both approaches achieved similar improvement in the transaortic hemodynamics post-TAVI (Table 3) and are consistent with the findings of other series [3, 23]. In addition, TAVI has been shown to provide superior hemodynamics comparable with that of stentless surgical bioprosthesis and yet with a lower risk of prosthesis-patient mismatch, as reported by Clavel and colleagues [23]. The transprosthetic gradients were similar in patients with TAVI and stentless surgical bioprothesis (10 mm Hg vs 9 mm Hg) but lower when compared with patients with stented surgical prostheses (13 mm Hg) [23].

The changes in LV dimensions and function observed in this study also reflect the improvements in transaortic hemodynamics post-TAVI. The LV mass reduced significantly and returned to within normal limits (113 ± 30 g/m^2) at 6 months or greater. In this respect, reduction in LV mass can occur as early as 5 days post-aortic valve surgery [24] and will continue even years postsurgery [7]. Although no significant changes in LV volumes or systolic function post-TAVI were noted in this study, changes in LV diastolic function were observed. The reduction in LV filling pressure and subsequent improvement of diastolic dysfunction post-TAVI were accompanied by a significant reduction in left atrial volume in our patients. Finally, consistent with previous studies [3, 25], paravalvular AR post-TAVI was not uncommon, with the majority of patients having mild AR postprocedure and remained stable over time in this study (Fig 3).

In summary, the present study shows that high-risk patients with severe AS can benefit from TAVI, in terms of favorable clinical outcomes and improved LV performance on echocardiography. These desirable changes can be observed early and at midterm follow-up. Comparing the approaches, the outcomes of TAA are comparable with that of TFA, but the TAA group has additional benefit of reduced radiation exposure and contrast use intraoperatively, without prolonging hospital stay. We acknowledge that this study was based on a relatively small patient cohort and reflects a single-center experience. In addition, selection bias associated with TAA (after TFA was denied) may form a limitation and patients who underwent TAA might potentially carry a higher perioperative risk, as compared with patients who underwent TFA. Nonetheless, this inherent difference would have biased the results toward a larger difference in outcomes, favoring that of TFA. On the contrary, this study showed that patients who underwent TAA had comparable early and midterm survival to those who underwent TFA.

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Summary and conclusions

SUMMARY AND CONCLUSIONS

The general introduction of this thesis (Chapter 1) outlines the epidemiology and the impact of aortic valve (AV) disease in the western world. The thesis further discuss the current and future role of advanced cardiac imaging modalities, using 3-dimensional (3D) echocardiography and speckle tracking echocardiography (STE) strain imaging in the diagnostic and clinical management of patients with aortic regurgitation (AR). In addition, the clinical applications of multimodality cardiac imaging in transcatheter aortic valve implantation (TAVI) for the treatment of severe aortic stenosis (AS) will be discussed: from pre-procedural patient evaluation, to the understanding of complications post-TAVI such as paravalvular regurgitation (PVR), and the assessment and monitoring of patients after TAVI.

Part I: Novel imaging to assess aortic valve regurgitation – incremental role in diagnosis

The first part of the thesis evaluates the incremental value of 3D echocardiograhy over the conventional 2-dimensional (2D) echocardiographic method to quantify AR, using 3D 3-directional velocity encoded magnetic resonance imaging (MRI) as the reference method (which has been proposed as an accurate method to assess transvalvular flow, after correcting for throughplane motion). Regurgitant volume obtained by 3D echocardiography showed excellent agreement with MRI, better than when comparing 2D echocardiography and MRI. When these two echocardiographic modalities are applied in the assessment of eccentric jets, 3D echocardiography showed a far better correlation with MRI (r=0.95), whereas the correlation with 2D echocardiography and MRI was weak (r=0.66). Therefore, quantification of AR using 3D echocardiography has shown to be superior to 2D echocardiography, particularly in patients with eccentric jets (**Chapter 2**). These observations are related to the fact that 3D echocardiography has the advantage of unlimited plane orientation, allowing the exact shape and size of the true cross-sectional view of the regurgitant orifice area to be planimetered, without any geometric or flow assumptions or multiple computation steps.

Chapter 3 evaluated the usefulness of myocardial strain imaging using 2D STE, in patients with chronic AR and baseline preserved left ventricular (LV) systolic function, and its predictive value of myocardial strain for future need of AV surgery was also assessed. In this evaluation, the extent of global longitudinal strain (GLS), circumferential strain and radial strain was calculated in each patient. Despite preserved LV ejection fraction (EF), multidirectional LV strain was more impaired in patients with chronic AR with symptoms than those without symptoms. In chronic AR, the LV adapts in the early course of the disease, normalizing wall stress and permitting normal filling pressures despite a substantial increase in LV volume overload. Hence, LVEF is normally preserved during the compensated phase, and many patients may remain asymptomatic for years. With time, the progressive LV enlargement and the increase in LV pressure will result in an increase in LV wall stress, and marks the onset of impairment in LV performance. New parameters such as myocardial strain, is more sensitive technique than LVEF to detect the subtle change in LV performance.

In the same chapter, in asymptomatic patients who were followed-up conservatively, GLS provided a significant incremental value over clinical and established echocardiographic predictors of poor outcome (including LV volume, parameters of AR severity) to predict those who are at risk of requiring AV surgery. Accordingly, GLS may serve as a potential screening tool in clinical risk stratification of asymptomatic patients with chronic AR and preserved LV ejection, in whom more aggressive follow-up and early intervention should be considered in patients with more impaired GLS.

PART II: ROLE OF MULTIMODALITY IMAGING IN TRANSCATHETER AORTIC VALVE IMPLANTATION – FROM SCREENING TO OUTCOMES

The second part of the thesis focuses on the clinical applications of multimodality cardiac imaging in TAVI for the treatment of severe AS. First and foremost, as opposed to conventional surgical aortic valve replacement (SAVR), direct visualization of the AV is lacking during the TAVI procedure. As a result, imaging becomes mandatory before the procedure, to ensure appropriate sizing of the valve prosthesis. Moreover, the best possible access to reach the valve, either via the transfemoral (TF), transapical (TA), transaortic or transsubclavian approach, needs to be evaluated carefully. Multidetector row computed tomography (MDCT), which has superior spatial resolution and 3D volumetric data sets, is capable of allowing unlimited plane reconstructions and thus, is a highly valuable screening modality in the pre-procedural work up of patients who are being considered for TAVI. **Chapter 4** summarizes the evolving role of MDCT in the patient selection and strategy planning of transcatheter valve intervention. Although transcatheter technology and its delivery and valve systems have improved over the years, and recent randomized studies have shown encouraging results with TAVI, there is still a high early risk of death and complications such as vascular complications, stroke, conduction block, coronary injury and PVR following the intervention. Some of these areas of concern can be minimized by careful patient selection, valve sizing and planning of the procedure. Therefore, the clinical application of multimodality imaging is proposed in the pre-TAVI evaluation algorithm (in **Chapter 5**), highlighting the important factors that need to be considered before the intervention.

Despite the combined effort of learning curve, advances in device technology and the better understanding of aortic root anatomy, AR remains frequent after TAVI. Accurate assessment of AR post-TAVI is clinically relevant since moderate to severe AR have been associated with poor clinical outcomes. In this respect, supra-aortic angiography and transesophageal echocardiography (particularly 3D echocardiography), is the preferred cardiac imaging technique to assess and to provide an evaluation of the mechanisms underlying AR immediately after valve deployment during the TAVI procedure (**Chapter 6**). This assessment step is crucial to decide whether additional maneuvers such as re-ballooning or valve-in-valve are needed to reduce the AR grade.

Severe AV calcification has been associated with PVR after TAVI due to bulky calcification that may prevent complete annular sealing by the deployed prosthesis, leaving gaps where the regurgitations jets may arise. **Chapter 7** highlighted that both the amount of AV calcification and its location (which can be visualized and quantified on pre-procedural MDCT) are important in determining PVR after TAVI. In particular, the amount of calcium at the valvular commissure and at the aortic wall could predict the occurrence of PVR, whereas the calcium at the valvular body or edge could not. The likely mechanism for this is that when there is significant amount of calcium present at the circumference of the native valve, it may prevent perfect apposition between the new transcatheter valve and the aortic wall, resulting in PVR at these sites.

Although many studies have reported worse clinical outcomes with significant AR immediately post-TAVI, there is limited data on how post-TAVI AR evolve over time. **Chapter 8** reported that significant AR (grade $\geq$2) appeared to improve over time, particularly within the first 6 months. Interestingly, significant PVR (grade $\geq$2) followed similar course with improvement over time, whereas intravalvular AR (AR within the prosthesis) remained unchanged over time. Importantly, patients who remained with significant AR (grade $\geq$2) at 6 months, continued to have negative impact on survival, when compared to those with AR grade <2.

Prosthesis-patient mismatch (PPM) occurs when the effective orifice area of a normally functioning prosthetic valve is too small in relation to the patient's body size. This phenomenon is not uncom-

mon in SAVR, particularly in patients with large body size and small aortic annulus. The incidence of at least moderate PPM (indexed effective orifice area $\leq 0.85 cm^2/m^2$) is 18% in our TAVI experience, and larger body size is a risk factor (**Chapter 9**). Similar to the experience of SAVR, PPM is also associated with less improvement in clinical functional status and less LV mass regression, together with persistent elevated LV filling pressure (as measured on serial echocardiography), when compared to patients without PPM after TAVI.

Finally, whether patients with depressed or preserved LVEF derive similar benefits from TAVI are explored in **Chapter 10**. Although higher perioperative and midterm mortality have been associated with patients with depressed LVEF undergoing SAVR, our experience showed that TAVI could be safely performed with similar procedural success in patients with LVEF <50% or ≥50% after careful preprocedural patient selection and screening. In fact, patients with baseline LVEF <50% showed marked LV reverse remodeling, with marked improvement in LVEF after TAVI. In the last **Chapter 11** of the thesis, the clinical outcomes and changes in cardiac performance on echocardiographic evaluations were compared between patients undergoing TAVI through a TF or TA approach. Not surprisingly, patients who underwent TF approach had more vascular complications, although the early, and midterm survival rates were comparable. Both groups achieved similar improvements in transvalvular hemodynamics and LV mass regression. Interestingly, patients with TA approach had significantly shorter fluoroscopy time and less use of contrast volume, when compared to patient with TF approach. A likely explanation for this observation is that less time is required for valve implantation via the TA approach due to better control of the device with a shorter distance between the AV and the apical access site.

CONCLUSIONS

Advanced cardiac imaging modalities play a central role in the diagnostic process and clinical management of patients with AV disease and in patients undergoing transcatheter AV therapy. In particular, 3D echocardiography is a very useful addition to cardiac imaging modality, which has demonstrated several advantages over the conventional 2D echocardiography, such as a more accurate assessment of valvular regurgitation, and the possibility of presenting real-time visualization of 3D cardiac structures with unlimited imaging plane, which is integral for guiding transcatheter valve intervention. Therefore, 3D echocardiography will be part of routine echocardiographic assessment of valvular heart disease. Myocardial strain imaging has also undergone tremendous development. With STE, it has become relatively easy to perform and is reproducible. In fact, GLS is now considered an established marker of global LV systolic function, which is far more sensitive and superior as compared to LVEF, and has prognostic value in patients valvular heart disease.

Finally, advanced multimodality imaging (combining echocardiography, MDCT and MRI) has provided superior anatomic and physiologic information that is crucial in the evaluation of patients with severe AS referred for transcatheter valve therapy. Post-procedural results and its impact on outcomes can also be accurately evaluated and monitored using advanced cardiac imaging over time, providing insights into the understanding of this relatively new therapy, which is regarded as an alternative to SAVR in high-risk patients.

Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

De algemene inleiding tot dit proefschrift (**Hoofdstuk 1**) beschrijft de epidemiologie en impact van aortaklep lijden in de Westerse wereld. Verder in deze thesis geven we de actuele en toekomstige rol van geavanceerde cardiale beeldvorming weer, waaronder de rol van 3D-echocardiografie en speckle tracking strain beeldvorming bij de diagnose en het management van patiënten met aortaklep lekkage. Bovendien worden klinische toepassingen van multimodaliteit beeldvorming bij transcatheter aortaklep implantatie (TAVI) ter behandeling van ernstige aortaklep stenose toegelicht: van pre-procedurele patiënt evaluatie tot het begrijpen van complicaties na TAVI zoals para-valvulaire lekkage, alsook de evaluatie en monitoring van patiënten na TAVI interventie.

DEEL I: NIEUWE BEELDVORMINGSTECHNIEKEN BIJ BEPALING VAN AORTAKLEP LEKKAGE – INCREMENTELE ROL BIJ DIAGNOSE

Het eerste deel van dit proefschrift evalueert de rol van 3D-echocardiografie versus conventionele 2D-echocardiografische technieken ter kwantificatie van aortaklep lekkage, gebruik makend van 3D *3-directional velocity encoded* magnetische resonantie imaging (MRI) als referentie methode. Deze techniek werd voorgesteld als een accurate methode om transvalvulaire flow te bepalen, na correctie van beweging doorheen het scanvlak. Excellente overeenkomst tussen het regurgiterend volume bekomen op basis van 3D-echocardiografie en MRI werd aangetoond, beter dan 2D-echocardiografie versus MRI. Wanneer deze twee echocardiografische modaliteiten worden toegepast bij de evaluatie van excentrisch verlopende jets, werd een significant betere correlatie tussen 3D-echocardiografie en MRI aangetoond (r=0.95), terwijl de correlatie tussen 2D-echocardiografie en MRI zwak bleek (r=0.66). Daarom besloten we dat kwantificatie van aortaklep lekkage op basis van 3D-echocardiografie superieur is versus 2D-echocardiografie, meer bijzonder bij patiënten met excentrische jets (**Hoofdstuk 2**). Deze observaties zijn gerelateerd aan het feit dat 3D-echocardiografie het voordeel biedt van een ongelimiteerde vlak oriëntatie, wat toelaat om planimetrie te doen van de exacte vorm en grootte van het ware cros-sectionele vlak van de lekkage oppervlakte, zonder geometrische of flow gebaseerde assumpties, noch multipele berekeningsstappen.

Hoofstuk 3 beschrijft het nut van myocardiale strain beeldvorming op basis van 2D speckle tracking echocardiografie bij patiënten met chronische aortaklep lekkage en initieel bewaarde kamerfunctie. Bovendien werd de predictieve waarde van myocardiale strain voor toekomstige noodzaak aan aortaklep heelkunde geëvalueerd. In deze studie werd de waarde van globale longitudinale strain (GLS), circumferentiële strain en radiale strain berekend bij elke patiënt. Ondanks bewaarde linker kamer ejectie fractie (LVEF), bleek multi-directionele strain gedaald in patiënten met chronische aortaklep lekkage. De linker kamer past zich vroeg in het ziekteverloop aan door normalisatie van de wand stress en het toelaten van normale vullingsdrukken ondanks een substantiële toename in linker kamer volume overbelasting. Daarom is de LVEF normaal behouden tijdens de gecompenseerde fase en blijven vele patiënten asymptomatisch gedurende multipele jaren. Na verloop van tijd zullen de progressieve linker kamer dilatatie en de verhoging van de linker kamer drukken uitmonden in een toename van de wand stress, wat het keerpunt vormt in het ontstaan van linker kamer performantie. Nieuwe parameters zoals myocardiale strain zijn veel gevoeliger dan LVEF om subtiele wijzigingen in linker kamer perfomantie te detecteren. In hetzelfde hoofdstuk, bij asymptomatische patiënten die conservatief werden opgevolgd, bood GLS een significante meerwaarde bovenop klinische en gevestigde echocardiografische predictoren van slechte uitkomst (waaronder linker kamer volume en parameters omtrent ernst van de aortaklep lekkage) om te voorspellen wie een risico heeft tot nood aan aortaklep heelkunde. Daarom zou GLS kunnen fungeren als een potentieel screening middel bij klinische risico stratificatie

van asymptomatische patiënten met chronische aortaklep lekkage en bewaarde linker kamer functie. In geval van meer gedaalde GLS, zou een meer agressieve opvolging en vroegtijdige interventie kunnen worden overwogen.

DEEL II: ROL VAN MULTI-MODALITEIT BEELDVORMING IN TRANSCATHETER AORTAKLEP IMPLANTATIE – VAN SCREENING TOT UITKOMST

Bij het tweede deel van dit proefschrift ligt de focus op klinische toepassingen van multimodaliteit beeldvorming bij TAVI bij behandeling van ernstige aortaklep stenose. Ten eerste en meest belangrijk, is directe visualisatie tijdens de TAVI interventie onmogelijk in tegenstelling tot conventionele heelkundige aortaklep vervanging. Hierdoor wordt beeldvorming voor een procedure dwingend, om adequate maatkeuze van de aortaklep prothese te faciliteren. Bovendien moet de best mogelijke route om de klep te bereiken zorgvuldig worden in kaart gebracht; trans-femoraal, trans-apicaal, trans-aortisch of via de arteria subclavia. Multi-detector computerized tomografie (MDCT) biedt superieure spatiale resolutie en de mogelijkheid tot 3D datasets en laat ongelimiteerde vlak reconstructies toe. Daarom is deze modaliteit uiterst geschikt bij de pre-procedurele uitwerking van patiënten die overwogen worden voor een TAVI ingreep.

Hoofdstuk 4 vat de evoluerende rol samen van MDCT voor patiënten selectie en strategie planning bij transcatheter klep interventie. Hoewel transcatheter technologie en diens delivery en klep systemen verbeterd zij over de jaren en recente gerandomiseerde studies bemoedigende resultaten voorgelegd hebben bij TAVI, blijft er nog steeds een hoog vroegtijdig risico op overlijden en complicaties zoals beroerte, geleidingsblok, coronaire beschadiging en para-valvulaire lekkage na interventie. Sommige van deze aandachtsgebieden kunnen geminimaliseerd worden door zorgvuldige patiënten selectie, klepmaat keuze en planning van de interventie. Daarom wordt de klinische toepassing van multimodaliteit beeldvorming naar voor geschoven in het pre-TAVI evaluatie algoritme (in **Hoofdstuk 5**), waarbij de belangrijkste factoren die dienen te worden overwogen voor een interventie worden aangestipt.

Ondanks de gecombineerde inspanning van leercurve, evoluties in device technologie en beter begrip van aortawortel anatomie, blijft aortaklep regurgitatie na TAVI een frequent probleem. Accurate bepaling van aortaklep lekkage na TAVI is klinisch uiterst relevant aangezien matige tot ernstige aortaklep lekkage geassocieerd is aan een slechte klinische uitkomst. In deze optiek zijn supra-aortische angiografie en slokdarm echocardiografie (voornamelijk 3D-echocardiografie) de technieken die preferentieel aangewend worden bij het vaststellen en de evaluatie van het mechanisme van aoartklep lekkage, onmiddellijk na de ontplooiing van de aortaklep prothese bij TAVI (**Hoofdstuk 6**). Deze bepaling is cruciaal om te beslissen of additionele manoevers zoals re-ballooning of klep-in-klep nodig zijn om de graad van aortaklep lekkage te reduceren.

Ernstige aortaklep calcificatie is geassocieerd aan para-valvulaire aortaklep lekkage na TAVI omdat omvangrijke calcificaties complete annulaire sealing door de ontplooide prothese kunnen tegenwerken, waarbij openingen ontstaan die aanleiding kunnen geven tot lekkage jets. **Hoofdstuk 7** onderstreepte dat zowel de hoeveelheid als de locatie van aortaklep calcificaties (die kunnen in het licht worden gesteld door pre-procedurele MDCT) belangrijke determinanten zijn van para-valvulaire lekkage na TAVI. Meer in het bijzonder konden de hoeveelheid calcium ter hoogte van de klep commissuren alsook de aortawand het ontstaan van para-valvulaire klep lekkage voorspellen, terwijl de calcium hoeveelheid ter hoogte van het klepblad lichaam of tip niet voorspellend bleek. De meest plausibele verklaring voor dit fenomeen is dat wanneer er een significante hoeveelheid calcium aanwezig is ter hoogte van de omtrek van de natieve klep, dit een barrière kan vormen om perfecte appositie tussen de nieuwe klep prothese en de aortawand te verzekeren, uitmondend in para-valvulaire lekkage op deze locaties.

Hoewel vele studies slechte klinische uitkomst gedocumenteerd hebben in geval van significante aortaklep lekkage onmiddellijk na TAVI, zijn data omtrent de evolutie van aortaklep lekkage na TAVI schaars. In **Hoofdstuk 8** documenteerden we dat significante aortaklep lekkage (≥ graad 2) bleek te verbeteren over verloop van tijd, voornamelijk gedurende de eerste 6 maanden. Een interessante bevinding was dat significante para-valvulaire lekkage (≥ graad 2) eenzelfde verloop kende met verbetering over tijd, terwijl intra-valvulaire lekkage (aortaklep lekkage binnenin de klepprothese) onveranderd bleef. Belangrijk is dat patiënten dewelke een significante aortaklep lekkage (≥ graad 2) behielden na 6 maanden, een minder gunstige overleving kenden in vergelijking met lekkage < graad 2.

Patiënt-prothese mismatch (PPM) ontstaat wanneer de effectieve klep openingsoppervlakte van een normaal functionerende prothese te klein is in relatie tot de lichaamsoppervlakte van de receptor. Dit fenomeen is zeker niet weinig frequent na chirurgische aortaklep vervanging, voornamelijk bij patiënten met een grote lichaamsbouw en een kleine aorta annulus. In onze TAVI ervaring bedraagt de incidentie van ten minste matige PPM (effectieve aortaklep openingsoppervlakte ≤ 0.85 cm^2/m^2) 18%, en grotere lichaamsbouw is hiertoe een risico factor (**Hoofdstuk 9**). Tevens is, net zoals bij de ervaring na heelkundige aortaklep vervanging, PPM geassocieerd aan minder verbetering van de klinische functionele status en minder linker kamer massa regressie, tezamen met persistente verhoogde vullingsdrukken in de linker kamer (gemeten door seriële echocardiografie), vergeleken met patiënten zonder PPM na TAVI.

Tot slot exploreerden we in **Hoofdstuk 10** of patiënten met een gedaalde versus bewaarde LVEF dezelfde voordelen ondervinden van TAVI interventie. Alhoewel hogere perioperatieve en mid-term mortaliteit geassocieerd is aan patiënten met gedaalde LVEF die chirurgische aortaklep vervanging ondergaan, toonde ons onderzoek aan dat TAVI veilig kon worden uitgevoerd met gelijkaardig procedureel succes bij patiënten met LVEF < 50% versus ≥ 50%, zorgvuldige patiënten selectie en screening in acht nemend. Patiënten met initieel LVEF < 50% toonden zelfs markante linker kamer reverse remodeling en verbetering van LVEF na TAVI.

In het laatste **Hoofdstuk 11** van dit proefschrift, vergeleken we de klinische uitkomst en veranderingen in cardiale performantie op basis van echocardiografische evaluaties bij TAVI patiënten die een trans-femorale dan wel een trans-apicale interventie ondergingen. Niet geheel onverwacht werden meer vasculaire complicaties vastgesteld bij trans-femoraal behandelde patiënten, hoewel de vroegtijdige en mid-term overleving vergelijkbaar bleken. Beide groepen bereikten vergelijkbare verbeteringen van de trans-valvulaire hemodynamica en linker kamer massa regressie. Een interessante vaststelling was dat we bij trans-apicaal behandelde patiënten een significant kortere fluoroscopie tijd noteerden en een lager contrast volume verbruik, in vergelijking met de trans-femoraal behandelde patientengroep. Een voor de hand liggende verklaring is dat minder tijd nodig is voor klep implantatie via een trans-apicale route omwille van betere device controle met tevens een kortere afstand tussen de aortaklep en de apicale toegangsplaats.

CONCLUSIES

Geavanceerde cardiale beeldvorming modaliteiten spelen een centrale rol bij het diagnostisch proces en het klinische management van patiënten met aortaklep aandoeningen, naast patiënten die een transcatheter aortaklep ingreep ondergaan. In het bijzonder is 3D-echocardiografie een zeer nuttige additionele beeldvormingstechniek dewelke multipele voordelen heeft aangetoond ten opzichte van 2D-echocardiografie. Enkele van deze voordelen omvatten meer accurate bepaling van klep lekkage en de mogelijkheid om real-time 3-dimensionele cardiale structuren te visualiseren met ongelimiteerde beeldvorming vlakken, wat cruciaal kan zijn bij begeleiding van transcatheter klep interventies. Daarom zal 3D-echocardiografie deel worden van routine evaluatie bij beoordeling van hartklep

aandoeningen. Myocardiale strain beeldvorming onderging tevens ook ingrijpende ontwikkelingen. Gebruik makend van speckle tracking technologie, is myocardiale strain beeldvorming relatief makkelijk geworden om uit te voeren en meer reproduceerbaar. GLS is thans een gevestigde merker van globale systolische linker kamer functie geworden, dewelke significant gevoeliger en superieur is vergeleken met LVEF en daarenboven duidelijk prognostische waarde heeft in patiënten met kleplijden.

Tot slot biedt geavanceerde multimodaliteit beeldvorming (waaronder een combinatie van echocardiografie, MDCT en MRI) de mogelijkheid tot vergaren van superieure anatomische en fysiologische informatie, dewelke een sleutelrol hebben bij de evaluatie van patiënten met ernstige aortaklep stenose die verwezen worden voor een transcatheter klep interventie. Bovendien kunnen post-procedurele resultaten en de impact op klinische uitkomsten eveneens accuraat beoordeeld en gemonitord worden door gebruik te maken van geavanceerde cardiale beeldvorming over verloop van tijd. Hierbij worden inzichten verworven ter begrip van deze relatief nieuwe therapie die als een alternatief kan worden beschouwd voor heelkundige aortaklep vervanging bij hoog risico patiënten.

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Curriculum Vitae

CURRICULUM VITAE

See Hooi Ewe was born on the 8th of December, 1976 in Taiping, Perak, Malaysia. She obtained her GCE 'O' and 'A' levels in Singapore. In 2002, she graduated from The University of Sydney with Bachelor of Medicine and Surgery (Honours Class I). Following her specialty training in internal medicine, she became a Member of the Royal College of Physicians, United Kingdom in 2005. Upon completion of advanced specialty training in Cardiology in 2009, she was admitted a Fellow of the Academy of Medicine, Singapore (Cardiology). In 2009, she was awarded the Ministry of Health (Singapore) Training scholarship and underwent a two-year cardiac imaging fellowship at the Leiden University Medical Center, Leiden, the Netherlands under the mentorship of Prof. Dr. Jeroen J. Bax. Over there, she learnt the applications of different cardiac imaging techniques to various clinical topics in the field of echocardiology (strain imaging and 3-dimensional imaging), cardiac computed tomography (in structural heart diseases) and magnetic resonance imaging (in the assessment of valvular diseases). In addition, her research interest focused on the application of advanced imaging in aortic valve diseases and percutaneous aortic valve therapy. The results of the fellowship are presented in this thesis. In September 2011, she returned to join the National Heart Centre Singapore (NHCS) as an Associate Consultant and was soon promoted to Consultant Cardiologist in 2011. Since returning from her fellowship, she has contributed significantly to NHCS and plays an instrumental role in developing NHCS capability in advanced imaging for structural heart interventions.