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Multimodality imaging assessment of the anatomy of the aortic valve apparatus in TAVI patients. Implications for prosthesis sizing and paravalvular regurgitation.

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Abbreviations

AO	Aortic
AoA	Aortic annulus
AoA-A	Aortic annulus area
AoA-D	Aortic annulus diameter
AR	Aortic regurgitation
AS	Aortic stenosis
AVA	Aortic valve area
AVAi	Aortic valve area normalized for body surface area
AVR	Aortic valve replacement
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CMR	Cardiac magnetic resonance
EDV	End diastolic volume
EDVi	End diastolic volume normalized for body surface area
EF	Ejection fraction
ESV	End systolic volume
ESVi	End systolic volume normalized for body surface area
EuroSCORE	European System for Cardiac Operative Risk Evaluation
LCC	Left coronary cusp
LM	Left main coronary
LV	Left ventricular
Max-D	Maximum diameter
MDCT	Multidetector computed tomography
Min-D	Minimum diameter
MPG	Mean pressure gradient
NYHA	New York Heart Association

PAR	Paravalvular aortic regurgitation
PPM	Patient prosthesis mismatch
RV	Right ventricular
TAVI	Transcatheter aortic valve implantation
TEE	Transesophaeal echocardiography
TTE	Transthoracic echocardiography

General introduction and Outline of the thesis

Introduction

Aortic stenosis (AS) has become the most frequent type of valvular heart disease in Europe and North America. As it primarily presents as calcific AS in adults of advanced age (2–7% of the population >65 years), its prevalence is expected to increase further in the future with an aging population. [1,2]

Severe AS is associated with debilitating symptoms (shortness of breath, angina, dizziness, or syncope), and reduced survival if left untreated. In fact it imposes a pressure overload on the left heart causing left ventricular hypertrophy, in turns leading to systolic and diastolic dysfunction, recognized risk factors for cardiac morbidity and mortality.

According to European Society of Cardiology guidelines, aortic valve replacement (AVR) is the definitive therapy for all patients with symptoms and severe AS, or severe AS with left ventricular systolic dysfunction. [3]

Traditionally, surgical AVR has been carried out with cardiopulmonary bypass, using either a mechanical or biological valve prosthesis. Valve sizing is performed intraoperatively using manufacturer specific sizing devices after excision of the native valve. However, approximately the 30% of patients referred for AVR are denied surgery because of advanced age, left ventricular dysfunction or comorbidities. [4] Treatment of high surgical risk patients has been modified with the introduction of transcatheter aortic valve implantation (TAVI) in 2002. [5-7] The procedure is performed off cardiopulmonary bypass via a percutaneous transarterial (usually transfemoral) approach or via a transapical approach by limited left thoracotomy. During the procedure a stent-mounted pericardial prosthesis is implanted within the native valve, displacing the native valve leaflets into the sinuses of Valsalva. Currently, both self-expanding and balloon expandable valve prostheses are commercially available and TAVI has been predominantly performed using either the balloon-expandable Edwards-Sapien valve (Edwards Lifesciences, Irvine, CA, USA) or the self-expanding Medtronic CoreValve device (Medtronic, Inc., Minneapolis, MN, USA), both of which have received CE Mark. [8,9]

The balloon-expandable Edwards-Sapien valve consists of three pericardial bovine leaflets mounted within a stainless steel tubular-slotted stent which has an outer diameter of 23 mm or 26 mm depending on the size of the valve (23 or 26 mm inflow). The following iteration (Sapien XT), provided in four sizes (20-23-26-29 mm), has a cobalt-chromium lower profile frame with an enhanced semi-closed leaflet design. A fabric cuff with an unscalloped construction at the inflow provides an effective seal for 7–8 mm of the stent, which is the target for placement across the aortic annulus (AoA). The valve is specifically designed to fit into the AoA and usually positioned below the coronary ostium. The latest iteration, Edwards Sapien S3, incorporates a stent and leaflet design that allows for crimping to a reduced profile as compared with the previous devices. As with these earlier devices, the inflow of the S3 is covered by an internal polyethylene terephthalate skirt. However, the S3 incorporates an additional outer polyethylene terephthalate cuff to enhance paravalvular sealing. This sealing cuff has no filling and functions like a parachute by bulging outward. [10]

The CoreValve is made of porcine pericardial tissue sewn to form a trileaflet valve mounted within an asymmetrical trilevel self-expanding nitinol frame. The lower portion of the frame affixes the valve to the left ventricle outflow tract, the mid-portion has a constrained waist that must be deployed at the level of the sinuses of Valsalva and coronary ostia and the upper section is designed to fix and stabilize the prosthesis in the ascending aorta. The Corevalve is designed for arterial access, generally performed through the femoral or subclavian artery, but direct aortic access is also an alternative and there are case reports of deployment using a transapical route. [10] Figure 1

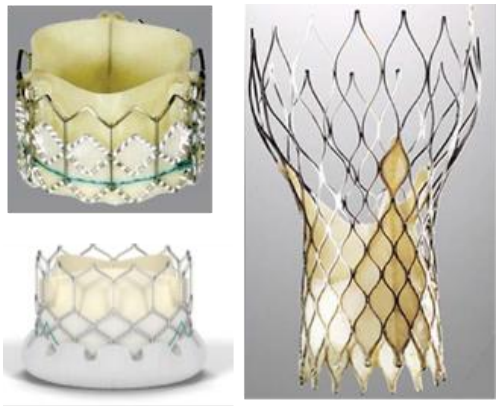

Figure 1. Left. Edwards Sapien Valve (up), Edwards Sapien S3 (bottom). Right. Medtronic Corevalve.

Clinical trials have shown TAVI to have outcomes similar to surgical AVR up to 2 years after the procedure and excellent outcomes have been confirmed by registry data, with overall survival of 76% at 1 year. [11-14] It is estimated that >100 000 TAVI have been performed between 2002 and 2014. It has

also become evident that clinical outcomes following TAVI are directly related to appropriate patient selection and valve choice.

Pre-procedure imaging is vital to assess the severity of AS, identify eligible candidates, plan the interventional approach, and select the appropriate prosthesis according to the anatomical features. Imaging is pivotal during and after the procedure, guiding prosthesis deployment, providing information regarding valve position, identifying immediate complications, and assessing outcomes.

Before TAVI, accurate measurement of the aortic root dimensions is essential for the selection of eligible candidates for the procedure and to ensure the appropriately sized valve prosthesis is chosen. Existing valves are designed for a specific range of annulus sizes and patients with annulus dimensions outside these ranges are not eligible for TAVI. Valve undersizing may lead to paravalvular regurgitation or device embolisation, while valve oversizing exposes the patient to the risk of aortic root rupture, significant conduction disturbance requiring pacemaker implantation or device underexpansion. Significant paravalvular aortic regurgitation (PAR) (greater than grade 2) is an independent predictor of late mortality in patients who undergo TAVI. [15] This parameter is the most commonly used outcome measure in TAVI sizing studies.

Once it has been determined that the patient has severe AS and from a clinical perspective is a suitable candidate for TAVI, detailed assessment of the aortic root is required and, in particular, AoA sizing is crucial for accurate selection of prosthesis size.

However, the AoA is not a true annulus in the sense of a fibrous ring surrounding the ventricular outflow tract and supporting the valve leaflets. There are several rings, at least 3 circular rings and 1 crown-like ring, to be found within the aortic root, not all corresponding to discrete anatomic structures. The annulus described by surgeons is usually the semilunar crown-like structure demarcated by the hinges of the leaflets. The valvar leaflets are attached throughout the length of the root. Seen in three dimensions, therefore, the leaflets take the form of a 3-pronged coronet, with the hinges from the supporting ventricular structures forming the crown-like ring. The top of the crown is a true ring, the sinutubular junction, demarcated by the sinus ridge and the related sites of attachment of the peripheral zones of apposition between the aortic valve leaflets. It forms the outlet of the aortic root into the ascending aorta. The semilunar hinges then cross another true ring, the anatomic ventriculoarterial junction. The base of the crown is a virtual ring, formed by joining the basal attachment points of the leaflets within the left ventricle. [16] Figure 2

This virtual annulus is not circular but rather elliptical in a large proportion of patients. [17,18] The shape of the annulus must be assessed in all patients, as eccentricity of the annulus is associated with a higher incidence of significant post-procedural PAR. Valve dimensions and geometry change during

the cardiac cycle, with root dimensions becoming larger and adopting a more circular conformation during systole. [19-21]

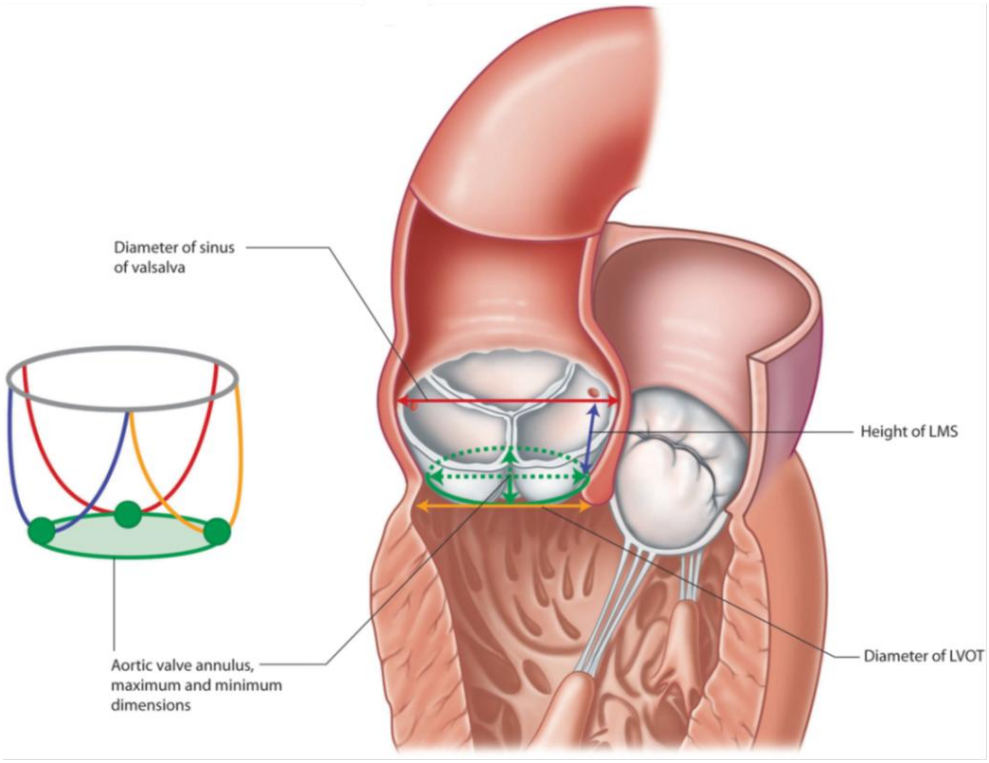

Figure 2. Model of the coronet shaped aortic valve annulus (left) and of the long-axis view of the left ventricle with examples of measuerments relevant to TAVI (right).

Further important aspects of imaging should be considered before TAVI. Particular considerations include leaflet morphology and extent and distribution of calcifications. Bicuspid valves have a more eccentric anatomy which may complicate valve positioning and lead to PAR. [22] The extent and distribution of calcification of the leaflets, sinuses, and the mitral valve annulus in the region of the mitral–aortic continuity must be assessed. Annular and commissural calcification and reduced annulus deformity is associated with a higher incidence of post-procedure PAR. [23] Extensive bulky calcification of the aortic valve leaflets may obstruct the coronary ostia, particularly in cases where the coronary ostia are low relative to the aortic annulus. [24]

In the majority of cases, the orifices of the coronary arteries arise within the 2 anterior sinuses of Valsalva, usually positioned just below the sinutubular junction. [16] It is not unusual, however, for the arteries to be positioned superior relative to the sinutubular junction. In a study of 51 normal postmortem hearts, the mean distance measured from the orifice of the left coronary artery to the basal attachment of the corresponding leaflet was 12.6±2.61 mm, and for the right coronary artery it was 13.2±2.64 mm. [25] Knowledge of the location of the coronary arteries, of course, is essential for

appropriate percutaneous replacement of the aortic valve. The valvar prostheses are designed such that a skirt of fabric or tissue is sewn within the stent or frame to help to create a seal and prevent paravalvar leakage. In situations in which the coronary arteries take their origin low within the sinus of Valsalva and/or the prosthesis is placed too high, the skirt may obstruct their orifices and thus impede coronary arterial flow. Furthermore, when the valve is deployed, it crushes the leaflets of the native valve against the aortic wall. The combination of a relatively low-lying coronary artery ostium and a large native aortic valvar leaflet therefore can obstruct the flow into the coronary arteries during valvar deployment. Thus, measurement of the height of the takeoff of the coronary arteries is important before valvar implantation. Figure 2

Several studies comparing different imaging modalities have been performed to assess TAVI sizing strategy. Traditionally sizing has been based upon a direct measurement of AoA diameter in the long axis plane by two-dimensional (2D) imaging techniques (transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or aortic contrast angiography). This method has limitations; these include the fact that they only measure the AoA in a single plane, with uncertainty as to whether the measurement plane is passing through the central point of the AoA. In addition, 2D methods assume circular annulus geometry despite a mounting body of evidence that this is not the case. Compared to 2D echocardiography, traditionally the gold standard, AoA measurements made by 3D imaging techniques (3D TEE, MDCT, MRI) may be more accurate. While there is strong correlation between these methods, there is a significant negative bias for 2D echo measurements as the measurements are traditionally made in the aortic long axis views, which do not correspond to the maximum dimension of the virtual basal ring; in fact, measurements made using the basal attachment of the leaflets do not transect the full diameter of the outflow tract but instead a tangent cut across the root. [17-19]

Moreover, coronary ostia impairment due to the presence of low coronary ostia and/or the occluding effect of aortic leaflets displacement by prosthetic percutaneous implantation is included between the possible life-threatening complications of the procedure. [24] The position of the coronary arteries relative to the AoA is evaluated traditionally using invasive angiography which is often performed in most of the patients preoperatively in order to study coronary arteries and peripheral vessels. However, the angiographic procedure shows the bias due to its 2D nature and in some cases it may carry an high risk of complications. Therefore MDCT has been reported as a valid alternative to angiography. However, it has also been demonstrated that the distance between the AoA and the left main ostium can be measured by 3D TEE. [26]

3D imaging techniques have also proved superior for the prediction of PAR in studies where valve sizing was based upon 2D echo. PAR is one of the most important predictors of morbidity and mortality after TAVI and, as such, is a commonly used outcome measure in clinical trials involving TAVI. The incidence and degree of PAR depend critically on the valve sizing. In fact, valve undersizing related to 2D-based AoA measurements may lead to significant PAR or valve embolization. [27-33] On the other hand, prosthesis oversizing has been associated with aortic root rupture and post-procedural conduction disturbance. [34,35]

Objective and outline of the thesis

The objective of this thesis is to investigate the incremental value of a multimodality imaging approach to the evaluation of the anatomy of the aortic valve apparatus in TAVI patients.

In **Chapter 1 to 3** feasibility and accuracy of 3D imaging modalities in the assessment of aortic valve apparatus in TAVI patients will be introduced. In particular, the 3D TTE and MRI feasibility and accuracy in the measurement of AoA will be explored. Thereafter, feasibility and accuracy of 3D TEE versus CT for the evaluation of AoA to left main ostium (LM) distance will be investigated.

Chapter 4 and 5 will discuss the additional prognostic value of 3D techniques (TEE and MDCT) in the prediction of PAR in TAVI patients.

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Chapter 1

Feasibility and accuracy of three-dimensional transthoracic echocardiography vs. multidetector computed tomography in the evaluation of aortic valve annulus in patient candidates to transcatheter aortic valve implantation.

Tamborini G, Fusini L, Muratori M, Cefalù C, **Gripari P**, Ali SG, Pontone G, Andreini D, Bartorelli AL, Alamanni F, Fiorentini C, Pepi M. *Eur Heart J Cardiovasc Imaging. 2014*

Abstract

Aims. Proper measurement of the aortic annulus (AoA) is crucial for the success of transcatheter aortic valve implantation (TAVI). Transthoracic echocardiography (TTE) is the first step to assess AoA diameter, but a two-dimensional TTE (2DTTE) measurement is no longer accepted as the sole determinant of prosthetic size. The aims of the study were to evaluate feasibility and accuracy of three-dimensional TTE (3DTTE) estimation of AoA dimensions in comparison with multidetector computer tomography (MDCT).

Methods and results. We enrolled 100 consecutive patients referred for TAVI. Feasibility of AoA evaluation was 91% for 3DTTE and in 90% for MDCT. In 81 of 100 patients, AoA maximum diameter (max-D), minimum diameter (min-D), and area were measured and compared using 2DTTE, 3DTTE, and MDCT. Image quality of 3DTTE was sufficient in 47, good in 46 and optimal in 7%. High correlations (P , 0.001) were found between MDCT and 3DTTE (max-D: r ¼ 0.89; min-D r ¼ 0.86; area: r ¼ 0.93), and between MDCT and 2DTTE (min-D: r ¼ 0.81; area 0.78). The 3DTTE measurements were found to be highly reproducible on intra- and interobserver variability analyses. Regarding the choice of prosthesis size, agreement between 3DTTE and MDCT was very good (k ¼ 0.84, P , 0.001) while it was poor between 2DTTE and MDCT (k ¼ 0.36, P , 0.001).

Conclusions. 3DTTE may be a valid imaging alternative in patients unsuitable for MDCT during the preoperative evaluation for TAVI. Evaluation of AoA through 3DTTE is feasible, and measurements closely approximate those of MDCT thus improving TTE accuracy in identifying the correct prosthesis size.

Introduction

Transcatheter aortic valve implantation (TAVI) has become a valid alternative to conventional surgery in selected high-risk patients. [1-4] However, a post-procedural paravalvular aortic regurgitation (PAR), has been frequently described. In the majority of patients PAR after TAVI is mild grade, while the incidence of moderate or severe PAR is low. [5-7] Although a mild PAR is known to be not associated with a dismal impact on left ventricular (LV) function and patient survival over the first year, recent reports have suggested that even a mild PAR could negatively impact mid- and long-term prognosis. [8-9] Valve sizing has been shown to be one of the strongest predictors of PAR, then an accurate pre-procedural evaluation of patients candidates for TAVI is mandatory to select the prosthesis size. [10-13]

Measurement of aortic annulus (AoA) dimension before TAVI has been traditionally and most commonly performed using transthoracic (TTE) and/or multidetector computed tomography (MDCT), while transesophageal echocardiographic (TEE) imaging (2D and 3D) is usually restrict to the intra-operative evaluation[14-23] and magnetic resonance imaging (MRI) is not a standard perioperative procedure even though is an accurate method. [24] However, up to 20% of patients undergoing TAVI cannot undergo to MDCT due to various contraindications. The accuracy of 2DTTE in defining AoA dimensions is lower in comparison to MDCT and 3DTEE. [25] Recently 3DTTE has been demonstrate to overcome 2D echo imaging limitations in different clinical settings. [26,27] The aim of this study was twofold: to assess feasibility and accuracy of 3DTTE compared to 2DTTE and MDCT for the measurement of AoA dimensions in the preoperatory evaluation of patients candidates to TAVI; to evaluate whether the 3 imaging methods impact differently on the choice of the prosthesis size.

Methods

Study population

From February 2013 to February 2014, 100 consecutive patients with severe symptomatic aortic stenosis were referred to our Institute for TAVI. Inclusion criteria were the presence of severe aortic valve stenosis (mean trans-aortic pressure gradient >40 mmHg or an aortic valve area <1cm^2) in cases with very high or prohibitive risk for surgical aortic valve replacement and a predicted post-implantation survival greater than 12 months. Exclusion criteria was the presence of a bicuspid aortic valve.

After a complete pre-procedural imaging (2DTTE, 3DTTE, MDCT and, when necessary, angiography to assess coronary, and aorto-ilio-femoral system) and clinical evaluation (assessment of operative risk, comorbidities, previous thoracic surgery or radiation and physical frailty) [27, 28] all the patients were evaluated by a multidisciplinary heart team including cardiologist, cardiac surgeon, interventional cardiologist, imaging specialist and cardiac anesthesiologist [19] to be finally admitted to the procedure.

In all patients, 2DTTE, 3DTTE and MDCT were performed within 48 hours each other and TTE preceded MDCT. The operators (echocardiographers and radiologists) were blinded to measurement of the other 2 modalities. TEE was perfomed only in cases undergoing TAVI.

Transthoracic echocardiography

TTE was obtained with patients in the left lateral decubitus position using a commercially available system (iE33 system, Philips Medical System, Andover, Massachusetts with a S5-1 sector array probe). Real-time 3DTTE was performed immediately after the 2D examination, with the same ultrasound unit, using an X3-1 matrix array probe. For each patient measurement of AoA diameter with 2DTTE (2DTTE min-D) was performed in systole in a parasternal long-axis view on the left ventricular outflow tract at the points of insertion of the right and non-coronary aortic leaflets (Figure 1). The 2DTTE AoA area was than calculated using the formula: $AoA=(2DTTE\ min\text{-}D/2)^2 \cdot \pi$, with the assumption that the AoA had a circular configuration.

Moreover, real-time zoomed 3D or full volume images containing the whole aortic apparatus were acquired for quantitative analysis. Measurements on 3D data sets were obtained off-line with a commercially available software package (3DQ, Q-Lab version 7.0, Philips Medical Systems).

The 3D dataset was analyzed moving 3 different orthogonal cut planes similarly to the published TEE recommendation method. [22] The final cut plane was transversal, oriented to visualize a short-axis view of the AoA, and on this plane the maximum diameter (max-D), the minimum diameter (min-D) were measured and AoA area were traced in systole. Figure 1

The quality of 3DTTE AoA reconstruction was graded as: (0) inadequate (these patients were not analyzed and excluded from the study), (1) sufficient (sufficient quality with rare artifacts), (2) good (good images without artifacts), (3) optimal (optimal images without artifacts).

Transesophageal echocardiography

Patients were imaged during TAVI procedure using a commercially available echocardiographic system (iE33, Philips Medical System, Andover, MA) equipped with a X7-2t probe, allowing 2D multiplane, real-time 3D and full volume TEE acquisitions. Accordingly to the current clinical practice,

a 2D acquisition in zoom mode of the left ventricular outflow tract from the mid-esophageal position with scanning planes from 115° to 160° was performed in order to assess precise measurements of AoA. Moreover, real-time zoomed 3D or full volume images containing the whole aortic apparatus were acquired. The 3D dataset was analyzed with the same modality used for 3DTTE for AoA evaluation and previously described.

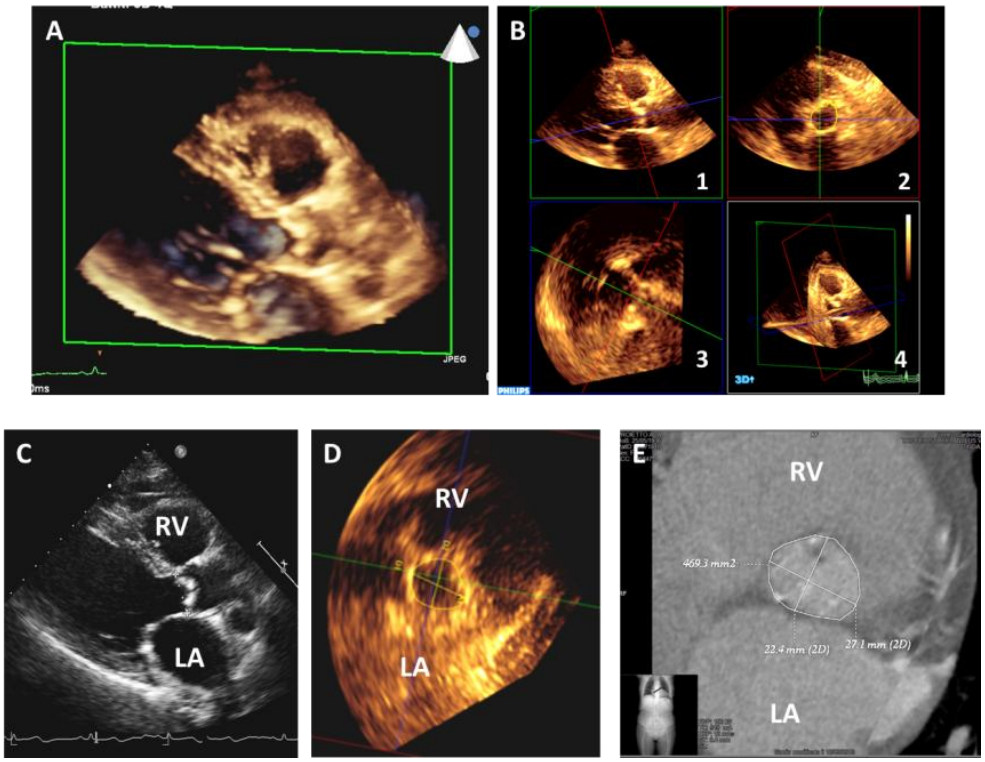


Figure 1. AoA measured by 2DTTE, 3DTTE and MDCT. Example of 3D TTE from the parasternal long axis view (A) and of AoA measurement. B. The 3D dataset was analyzed through 3 different orthogonal cut planes: red plane (1) is a short-axis view of aortic root crossing AoA; green (2) and blue (3) planes are sagittal views of the ascending aorta. The red plane was shifted from aortic root towards left ventricular outflow tract until aortic valve cusps disappeared, allowing the measurement of the AoA. (4) The position and the relationship of each plane in the 3D dataset are shown. C. AoA diameter measured by 2DTTE in a parasternal long axis view. AoA minimum diameter, maximum diameter and area measured in a cross-sectional plane of a 3DTTE (D) and multidetector computed tomography (MDCT, E) dataset. RV = right ventricle, LA = left atrium.

Multidetector computed tomography

All examinations were performed with a Discovery HD750 scanner (GE Healthcare, Milwaukee, Wisconsin). Scanning parameters were: slice configuration, 64 x 0.625mm; gantry rotation time, 350ms; tube voltage, 120 kVp; and effective tube current, 650mA. Contrast enhancement was achieved with a triphasic injection of an 80-mL bolus of Iomeron 400mg/mL (Bracco Imaging S.p.A., Milan, Italy) through an antecubital vein at a 5-mL/s infusion rate, followed by 50 ml of saline

solution, and a further 50-mL bolus of contrast at 3.5mL/s. After the threshold level of 200 Hounsfield units (HU) in the right ventricle was achieved, patients were instructed to hold a deep breath, and the scan was started when a threshold of 200 HU was reached in the left atrium, allowing the synchronization of the arrival of the contrast media and the scan. Data acquisition was performed with retrospective electrocardiogram triggering. Image analysis was performed on a separate computer workstation. AoA was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets. [13] max-D, min-D, and the area of AoA were measured in an orthogonal plane on the center line of the aorta in systole.

Prosthetic valve sizing

To evaluate the difference on TAVI strategy we indicated the theoretical prosthesis size based on 2D and 3D AoA measurements compared to MDCT values as gold standard. The SAPIEN XT valve (Edwards Lifesciences Inc, Irvine, California) in 3 different sizes (23-, 26-, and 29-mm expanded diameter) was considered. Currently there is no consensus regarding the gold standard imaging technique for AoA sizing. From a practical perspective the choice of the prosthesis size was made according to guidelines, [18-20] in particular the size was primary chosen depending of AoA diameters and, secondary, in the uncertain cases, on the base of AoA area. Our current practice was to use both MDCT and echocardiographic data for sizing and the interventionist/surgeon in the event of discrepancy decided on the basis a) of her/his experience related to the specific prosthetic model, b) of the method that provided the best image and c) of other technical details (vascular accesses, coronary-aortic annulus distance, angiography).

Statistical analysis

Data are presented as mean and standard deviation for continuous variables, while categorical variables are presented with frequencies and relevant percentages. Normality of distributions for continuous variables was tested using the Kolmogorov-Smirnov test. Linear regression analysis with Pearson correlation coefficient was used to evaluate the relationship between 3DTTE and MDCT AoA measurements. Bland-Altman analysis was used to assess the inter-technique agreement by calculating the bias (mean difference) and the 95% limits of agreement (defined as 1.96SD around the mean difference). To assess the reproducibility of the 3DTTE measurements, intraobserver and interobserver variability were evaluated in a subset of 25 randomly selected patients. Each parameter was reevaluated ≥2 weeks later on the same 3DTTE dataset by the main investigator and by a second investigator who was blinded to the results obtained by the main investigator. Both intraobserver and interobserver variability are reported in terms of intraclass correlation coefficients (ICCs) and

coefficients of variation (CV, percentages). Moreover, Bland-Altman analysis was applied to evaluate the limits of intraobserver and interobserver agreement. The Cohen K statistic was used to assess agreement between 2DTTE, 3DTTE and MDCT prosthesis size indication. All statistical analyses were carried out with SPSS 20.0 (SPSS Inc., Chicago, IL).

Results

Clinical and echocardiographic characteristics of the study population are summarized in Table 1. Of the 100 consecutive patients enrolled, 19 were excluded from the study for inadequate echocardiographic window (9 patients) or inability to obtain MDCT data for renal impairment or tomographic poor image quality due to atrial fibrillation, arrhythmias or tachycardia (10 patients). Therefore feasibility of AoA measurements was 90% for MDCT and 91% for 3DTTE and finally 81 patients constituted our study population.

Table 1: Clinical and echocardiographic characteristics of the study population (n=81).

Variable	
Male (%)	38 (47%)
Age (years)	81±7
Body surface area (m^2)	1.75±0.20
Logistic EuroSCORE (%)	20.8±12.1
Aortic valve area index (cm/m^2)	0.69±0.13
Aortic peak systolic gradient (mmHg)	81±24
Aortic mean systolic gradient (mmHg)	49±16
Left ventricular diastolic volume index (ml/m^2)	56±22
Left ventricular systolic volume index (ml/m^2)	26±22
Left ventricular ejection fraction (%)	59.9±11.9
Left ventricular mass index (g/m^2)	151±46
Aortic regurgitation (1-4)	1.7±0.8
Systolic Pulmonary pressure (mmHg)	41±12

Values espressed as mean±SD or absolute count(%).

The quality of 3DTTE AoA imaging was sufficient in 38 cases (46.9%), good in 37 cases (45.6 %) and optimal in 6 cases (7.5%).

Evaluation of aortic annulus dimensions

Mean value of AoA measurements and correlation between each methods are shown in Table 2. Significant correlations were found both between 3DTTE and MDCT and between 2DTTE and MDCT.

Table 2. Mean values of aortic annulus measurements.

	3DTTE	MDCT	2DTTE	r_1	p_1 Value	r_2	p_2 Value
Min-D (mm)	21.5±2.3	21.4±2.4	21.5±2.2	0.86	<0.001	0.81	<0.001
Max-D (mm)	25.5±3.0	26.5±3.1		0.89	<0.001		
Area (mm^2)	443.2±97.0	442.5±94.8	367.3±76	0.93	<0.001	0.78	<0.001

Values espressed as mean±SD or absolute count(%).

A significant correlation was also found between 3DTTE and MDCT AoA max-D measurements. In the evaluation of AoA area an excellent correlation was demonstrated between 3DTTE and MDCT. Besides 2DTTE underestimation of AoA area in comparison with MDCT, a good correlation between the 2 methods was observed . Figure 2 shows correlations between 3DTTE and MDCT AoA measurements together with the results of Bland Altman analysis . The quality of 3DTTE imaging did not affect these correlations.

3DTEE was performed in 43 out of 52 patients who underwent TAVI (9 cases were excluded for contraindications to TEE or because the procedure was performed without TEE monitoring). A significant correlation was found between 3DTEE and MDCT AoA measurements (3DTEE max-D 25.3±2.7mm, r=0,78, p<0.001; min-D 21.5±2.3mm, r=0.86, p<0.001; area 440.1±98mm^2, r= 0.91; p< 0.001) and between 3DTEE and 3DTTE (max-D: r=0.82, p<0.001; min-D: r= 0.83, p<0.01; area: r= 0.90, p<0.001).

Intra- and inter-observer variability

The 3DTTE measurements was found to be highly reproducible in terms of intra-observer variability both using ICCs (min-D, 0.83; max-D, 0.81; Area, 0.91) and CV (min-D, 2.8%; max-D, 3.2%; Area, 3.3%). Similar results were obtained for the inter-observer variability analysis (ICCs: min-D, 0.85; max-D, 0.81; Area, 0.91; CV: min-D, 3.3%; max-D, 3.0%; Area, 3.8%). The results of Bland-Altman analysis of the agreement between repeated measurements of min-D, max-D and area are depicted in Figure 3.

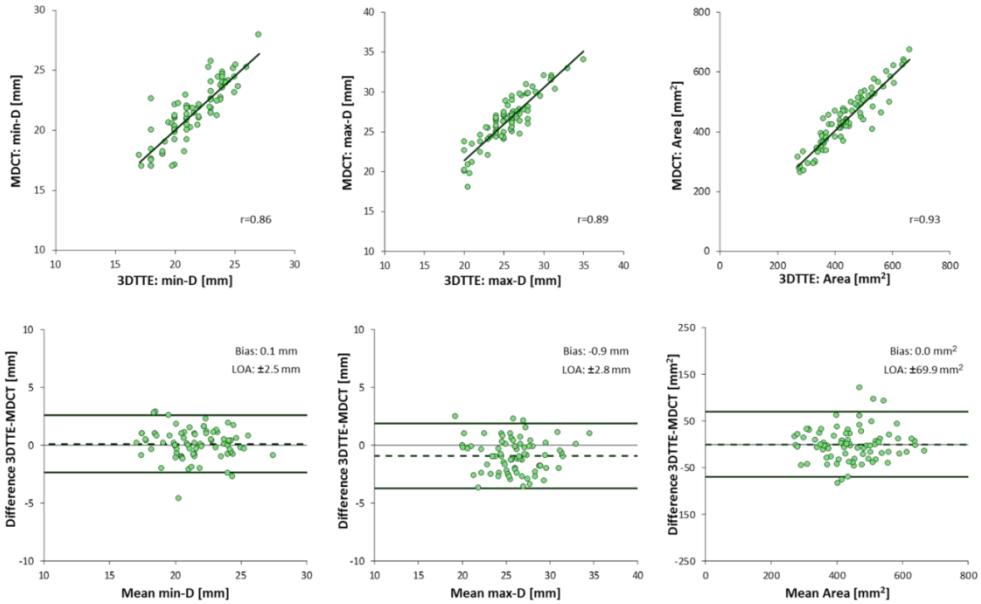


Figure 2. 3DTTE and MDCT Correlations and Agreements. Results of linear regression (top panels) and Bland-Altman analysis (bottom panels) for, from left to right, minimum aortic annulus (AoA) diameter (min-D), maximum AoA diameter (max-D), and AoA Area measured by 3DTTE and MDCT. The dashed lines represent bias and the solid lines±1.96 standard deviation. LOA, limits of agreement.

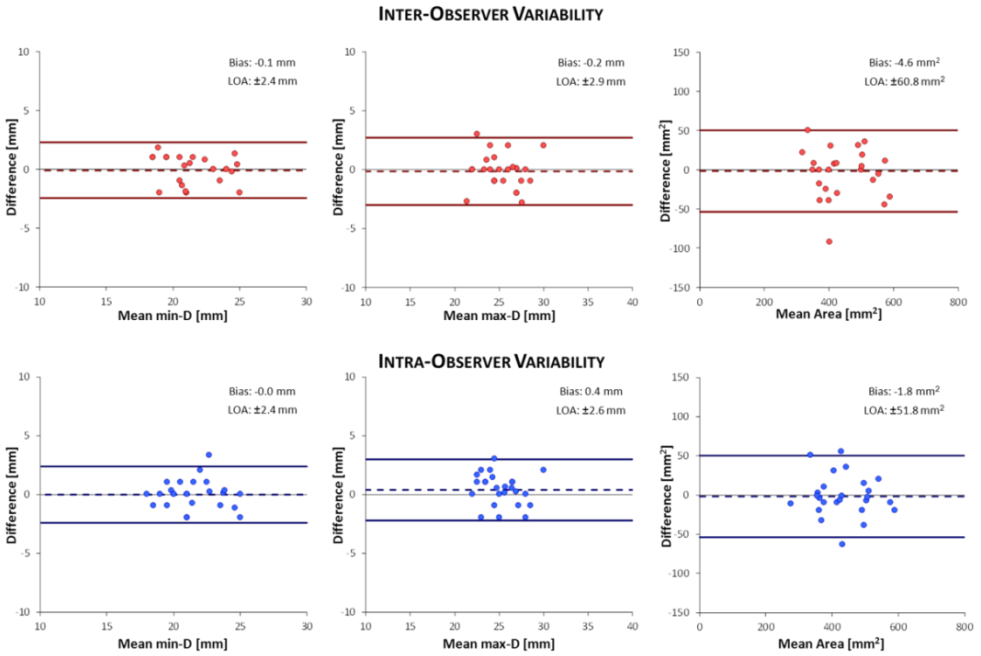


Figure 3. Inter-observer and Intra-observer Variability. Results of Bland-Altman analysis of the agreement between repeated measurements of minimum aortic annulus (AoA) diameter (min-D), maximum diameter (max-D), and Area for inter-observer (top) and intra-observer (bottom) variability applied to 3DTTE images obtained in a subset of 25 randomly selected patients. The dashed lines represent bias and the solid lines±1.96 standard deviation. LOA, limits of agreement.

Theoretical impact of the 3 methods on the choice of prosthetic size

Results of the theoretical impact of the measurements of aortic annulus dimensions using 2TTE, 3DTTE and MSCT on the decision to perform TAVI procedure and to the selection of prosthesis size are shown in Figure 4. Agreement between 3DTTE and MDCT was higher (k=0.82) in comparison with agreement between 2DTTE and MDCT (k=0.34). The 3 cases with a too small AoA and the 2 cases with too larger AoA were correctly identified by 3DTTE vs MDCT. On the contrary 2DTTE was inaccurate in the evaluation of 1 too large and 1 too small cases. As concern prosthetic sizing 3DTTE was in agreement with MDCT in 89% and showed undersizing or oversizing in 3% and 6% patients, respectively.

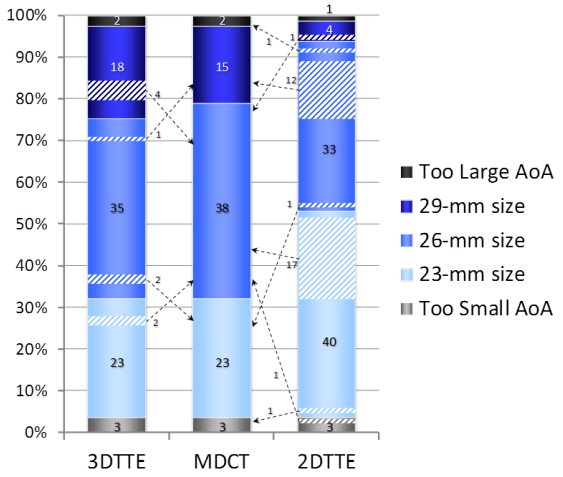
On the contrary, 2DTTE agreed in MDCT prosthesis sizing in 47/81 cases (58%), while an undersizing was observed in 30 (37%) and oversizing in 4 (5%) patients.

Choice of prosthetic size and clinical outcomes in patients undergoing TAVI

Of the 81 patients included in the study 52 underwent to TAVI. For clinical or anatomical contraindications TAVI procedure was denied in 29 cases: in 13 a surgical prosthesis was implanted, in 3 a percutaneous balloon valvuloplasty was performed and in 13 medical therapy was maintained.

In 45 out of 52 cases the implanted prosthesis size was concordant with MDCT and 3DTEE data. In one case the interventionist/surgeon based the decision on measurements suggested by MDCT (29mm) while 3DTTE indicated a lower size (26mm). In 5 cases the implanted prosthesis was oversized in comparison to MDCT data, while in one case was undersized (a 23-mm prosthesis was implanted despite both MDCT and 3DTTE suggested a 26-mm model). Successful TAVI was reached in all patients. No in-hospital death was observed.

After the procedure PAR was absent or trivial in 26 cases (50%), mild in 15 (29%), mild/moderate in 11 (21.2%). No patient had moderate/severe regurgitation. The incidence and degree of severity of PAR were not different in cases in whom the interventionist/surgeon decided in accordance or discordance with 3DTTE or MDCT data, but this analysis was limited by the small sample size.



	Patients, n (%)	k Cohen
3DTTE vs MDCT		
Concordant Size	72/81 (89%)	0.84 (p<0.001)
Undersizing of 3DTTE vs MDCT	3/81 (4%)	
Oversizing of 3DTTE vs MDCT	6/81 (7%)	
2DTTE vs MDCT		
Concordant Size	47/81 (58%)	0.36 (p<0.001)
Undersizing of 2DTTE vs MDCT	30/81 (37%)	
Oversizing of 2DTTE vs MDCT	4/81 (5%)	

Figure 4. Relationship between prosthesis size indication based on 3DTTE, MDCT, and 2DTTE measurements. MDCT was used as gold standard. The areas filled with a diagonal line pattern represent the number of patients with a different choice of the prosthesis size compared to MDCT. Dotted arrows indicate the actual MDCT size for those patients with a discordant size by 2DTTE and 3DTTE measurements. The absolute number and relative percentages of concordant size, undersizing and oversizing of 3DTTE and 2DTTE vs MDCT was reported in the table.

Discussion

Accumulating data have reported promising results concerning procedural success, quality-of-life improvement, and short-, mid-, and more recently long-term outcomes after TAVI in high-risk patients with severe aortic stenosis. [1-5] However, aortic regurgitation, mainly paravalvular, has been described in a relatively large number of patients after TAVI. The presence of significant, or even mild, PAR is an independent risk factor for mortality at short- and mid-term follow-up. [6-9] Incorrect valve sizing (together with commissural calcifications) has been proven to be the principal cause for postoperative PAR as well as it is known to be the principal guilty for severe complications such as annular ruptures. [10-13] Thus, an accurate anatomical evaluation and correct sizing of the AoA are mandatory for patient selection and prosthetic size choice.

Even though there are large series of cases with different imaging modalities, there is no consensus regarding the ideal imaging method for AoA sizing and preoperatively a multimodal

assessment is suggested. Besides in guidelines [18-20] TTE, TEE and MDCT are all imaging modalities recommended as work-up study before TAVI, TEE in a conscious, or mildly sedated, patient may be frequently poorly tolerate in more critically cases and should be performed very carefully. For this reason in the preoperative phase 2DTTE and MDCT are routinely used, while TEE with fluoroscopy and angiography are generally reserved to the perioperative phase in the procedural setting.

Moreover, AoA is not a circular ring but is a complex structure with an oval cross sectional shape. A 2D evaluation of AoA dimensions through 2DTTE or 2DTEE diameters fails to appreciate its elliptical geometry, whereas 3D imaging methods as MDCT or 3DTEE can overcome this limitation.[25]

The accuracy of MDCT in identifying the correct prosthesis size has been well demonstrated and this is one of the most important reasons why MCDT may be considered the reference method, allowing a comprehensive evaluation not only of AoA morphology, but also of peripheral, carotid and coronary circulation.[15,18,21]

The higher accuracy of 3DTEE in comparison to 2DTEE in the analysis of the AoA (using MDCT as gold standard) has been extensively proved. [18,29,30] A previous research of our group [17] showed that 3DTEE was a valid modality for the measurement not only of AoA dimensions but also of left coronary cusp length and of the distances from left main coronary ostium to the AoA, in a large TAVI population. Recently in a “in vitro” model, MRI was also demonstrated to be the most accurate method for assessing the dimensions of the ring models. [31] In a clinical setting, Pontone [25] confirmed that aortic root assessment with MRI including AoA size, aortic leaflet length, and coronary artery ostia height is accurate compared with MDCT.

To the best of our knowledge, data on 3DTTE in this field are lacking. Doddamani et al. [32] compared 3DTTE and 2DTTE in the evaluation of LV out flow tract anatomy and dimensions in 53 normal subjects and demonstrated that 3DTTE reconstruction of LV outflow tract is feasible and discussed the addition value of 3DTTE in aortic valve area estimation due to the use of LV outflow tract planimetric area in continuity equation.

This is the first study aimed at the evaluation of 3DTTE analysis of AoA in patients with severe aortic stenosis undergoing a screening evaluation for TAVI. The main findings of our study are: a) 3DTTE evaluation of AoA is feasible in the majority of the patients with low intra and inter observer variability; b) 3DTTE and MDCT measurements did not differ significantly, with excellent agreement in the selection of cases with too small or too large AoA (exclusion criteria for TAVI) and a good agreement in the choice of prosthetic size in cases scheduled for the procedure.

In our study population feasibility of MDCT and 3DTTE were similar (89% vs 90% respectively) and 3DTTE images were good or optimal for AoA measurement in 43/81 cases. In the remaining 38

cases despite suboptimal resolution of 3DTTE , AoA planimetric area and diameters outline were possible in all of them.

Even though it is well know that MDCT provides precise information about the AoA anatomy and it is considered the gold standard for the pre-operative assessment of TAVI candidates, not all the patients can be studied by MDCT for several reasons such as impaired renal function, severe breathlessness, and arrhythmias. MRI has been demonstrated to be a valid alternative in these cases, however in a recent series[25] from the original population of 80 consecutive TAVI patients, 30 were excluded being unsuitable candidates for one or both the procedures (MDCT and MRI).

Three-dimensional TTE does not require breath-old and contrast infusion, may be obtained at the bedside, in more critical cases, and also in the presence of arrhythmias. In fact, the area of interest is limited to the aortic apparatus and can be completely contained in a 3D live format avoiding multibeat full volume acquisition. The most important limit of the method is the dependency to the acoustic window of the patient. In our population an inadequate acoustic window was found in 9 out of 90 cases. In the 10 out of 100 cases who could not undergo to MDCT (3 for renal impairment and 7 for arrhythmias), the preoperative AoA evaluation was obtained through 2D and 3DTTE and the correct prosthesis size was confirmed intra-operatively by 2D and 3DTEE.

In the present study, no significant differences have been observed between 3DTTE and MDCT AoA measurements. On the contrary while no significant differences were present between all the 3 methods in the evaluation of AoA min-D, the 2DTTE AoA area, geometrically derived from 2DTTE diameter, was considerably lower in comparison both with 3DTTE and MDCT planimetric surface area. These results may be expected due to the oval shape of AoA, with significant differences between maximum and minimum diameter that is generally observed in a antero-posterior position corresponding to the 2DTTE estimated diameter. Thus the geometrical derived 2D area (derived from AoA min-D) amplifies the difference between 2D and 3D modalities. Moreover, in a minority of cases of our series 3DTEE was also performed. As previously demonstrated[14-18] our data confirm an excellent correlation between 3DTEE and MDCT AoA measurements. As expected in this subgroup we also found a very high correlation between 3DTTE and 3DTEE data, thus reinforcing the concept that 3D modalities were superior in measurements of AoA in comparison with the corresponding TTE and TEE 2D techniques.

Clinical implications

Accurate AoA measurements are critical for patient selection and successful valve implantation. While 2DTTE and 2DTEE have been the primary methods for AoA measurements, nowadays MDCT is

considered as the reference standard. The ability to manipulate imaging planes for AoA measurements is the main reason of MDCT accuracy. In this regard the potential of 3DTTE has been underappreciated. Our data demonstrate that 3DTTE (confirming 3DTEE data) [16-18,22,23] may easily allow AoA measurements. It may be proposed as a screening test not only for aortic valve stenosis diagnosis (inside a comprehensive 2D and Doppler examination) but also to identify too small or too large AoA and to indicate the presumable size of the different TAVI models. This is particularly useful in cases in whom MDCT or MRI are not suitable. Therefore, 3DTTE may be a gatekeeper to the procedure and in the different settings MDCT, MRI and 3DTEE may be utilized depending on the local strategies. Moreover the simplest method (2DTTE and 3DTTE) may be utilized in centers which do not perform TAVI and in which more advanced methodologies are not present to preselect candidates with severe aortic stenosis and high risk for surgery.

All these data are in agreement with previous studies on 3DTEE vs. 2DTEE showing that 3DTEE provide more accurate information that 2DTEE with superior discrimination of post-TAVI regurgitation.[7,12,33]

Study limitations

This study is not a randomized one, however it includes a consecutive series of patients undergoing a multimodality imaging screening before TAVI. Only 52 out of 81 cases underwent the procedure. Therefore, imaging measurements allowed us to compare values of the different modalities in all cases evaluating the theoretical impact on the choice of prosthetic size and clinical outcomes and choice of the implanted prosthetic size in only 52 patients undergoing TAVI.

3DTEE was performed in a subgroup of patients. Despite we could not perform a complete analysis and head-to-head comparison in all our cases (this was behind the scope of this study) measurements with 3DTEE showed an high correlation with both 3DTTE and MDCT values.

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Chapter 2

Comparison of accuracy of aortic root annulus assessment with cardiac magnetic resonance versus echocardiography and multidetector computed tomography in patients referred for transcatheter aortic valve implantation.

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Abstract

The evaluation of the aortic root in patients referred for transcatheter aortic valve implantation is crucial.

The aim of the present study was to compare the accuracy of cardiac magnetic resonance (CMR) evaluation of the aortic annulus (AoA) with transthoracic and transesophageal echocardiography and multidetector computed tomography (MDCT) in patients referred for transcatheter aortic valve implantation.

In 50 patients, maximum diameter, minimum diameter and AoA, length of the left coronary, right coronary, and noncoronary aortic leaflets, degree (grades 1 to 4) of aortic leaflet calcification, and distance between AoA and coronary artery ostia were assessed.

AoA maximum diameter, minimum diameter, and area by CMR were 26.4 – 2.8 mm, 20.6 – 2.3 mm, 449.8 – 86.2 mm2, respectively. The length of left coronary, right coronary, and noncoronary leaflets by CMR were 13.9 – 2.2, 13.3 – 2.1, and 13.4 – 1.8 mm, respectively, whereas the score of aortic leaflet calcifications was 2.9 – 0.8. Finally, the distances between AoA and left main and right coronary artery ostia were 16.1 – 2.8 and 16.1 – 4.4 mm, respectively.

Regarding AoA area, transthoracic and transesophageal echocardiography showed an underestimation ($p < 0.01$), with a moderate agreement (r: 0.5 and 0.6, respectively, $p < 0.01$) compared with CMR. No differences and excellent correlation were observed between CMR and MDCT for all parameters (r: 0.9, $p < 0.01$), except for aortic leaflet calcifications that were underestimated by CMR.

In conclusion, aortic root assessment with CMR including AoA size, aortic leaflet length, and coronary artery ostia height is accurate compared with MDCT. CMR may be a valid imaging alternative in patients unsuitable for MDCT.

Introduction

Accurate measurement of the aortic annulus (AoA) is essential for appropriate valve sizing in transcatheter aortic valve implantation (TAVI). Measurement of AoA before and during TAVI has been traditionally and most commonly performed using transthoracic (TTE) and transesophageal (TEE) echocardiography. However, multi-detector computed tomography (MDCT) has distinct advantages over 2D echocardiography such as exceptional spatial resolution and multiplanar reformatting capabilities and has demonstrated to be a feasible and accurate imaging modality for the evaluation of the aortic root morphology and dimensions that may influence or modify TAVI strategy in a considerable number of cases.[1-5] Unfortunately, up to 20% of patients undergoing TAVI have clinical conditions that make them unsuitable candidates for MDCT [1]. Moreover, MDCT requires contrast agent administration that may be a hazard issue in patients with reduced kidney function who are a substantial proportion of TAVI patients.[6, 7]

Cardiac magnetic resonance (CMR) does not need administration of contrast agents, provides similar 3D multi-slice images of the aortic root and may be a valid alternative to MDCT. However, only few data are available regarding its accuracy in comparison with MDCT.[8-10] Thus, the aim of this study was to assess feasibility and accuracy of CMR in comparison with MDCT for the evaluation of AoA, aortic leaflets length and AoA-coronary artery ostia distance in patients referred for TAVI.

Methods

Between January 2011 and June 2012, 80 consecutive patients with severe aortic stenosis were referred to our institute for TAVI. Exclusion criteria were severely impaired renal function (creatinine clearance <30 ml/min) (4 patients), inability to sustain a 10-s breath hold (2 patients), atrial fibrillation or other cardiac arrhythmias (9 patients), presence of pacemaker or intracardiac defibrillator (10 patients) and claustrophobia (5 patients). According to the exclusion criteria, a total of 50 patients were included in the study (27 men, mean age 79.62$\pm$7.52 years, logistic Euroscore 22.4$\pm$8). Written informed consent was obtained from all patients and the study protocol was approved by the local ethical committee.

TTE was obtained with patients in the left lateral decubitus position using a commercially available system (IE33 system, Philips Medical System, Andover, MA) in the parasternal (long- and short-axis) and apical (2- and 4-chamber) views at baseline.

For each patient, end-diastolic and end-systolic left ventricle volumes were measured. Left ventricle ejection fraction was calculated by echocardiography biplane Simpson's rule. The severity of aortic stenosis was assessed by the peak and mean aortic gradients, while the aortic valve area was calculated with the continuity equation. The aortic stenoses was graded according to the American College of Cardiology/American Heart Association guidelines.[11] Regurgitation of the mitral and aortic valves was graded as none (grade 0), mild (grade 1), mild to moderate (grade 2), moderate (grade 3) or severe (grade 4) according to published guidelines. [11]

Measurement of AoA diameter by TTE was performed in systole in a parasternal long-axis view on the left ventricular outflow tract at the points of insertion of the right and non-coronary aortic leaflets (Figure 1). The AoA area by TTE was estimated using the following equation: (AoA-diameter/2)2 * Π with the assumption that the AoA had a circular configuration.

All patients underwent TEE (IE33 system, Philips Medical System, Andover, MA) with a multiplane probe in the mid-esophageal position at 110–135° for full visualization of the AoA. TEE measurements of AoA diameter and area (Figure 1) were obtained in the same way as described for TTE. TTE was repeated after TAVI before patient discharge and at 1 month.

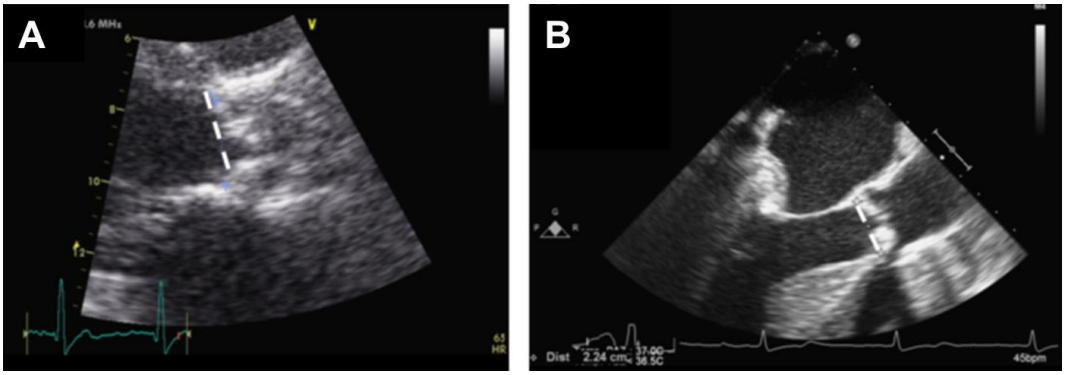

Figure1. Methodology for the assessment of the AoA using TTE and TEE. TTE (Panel A): the AoA diameter is measured in a parasternal long-axis view on the left ventricular outflow tract at the point of insertion of the right and non-coronary aortic leaflet in mid-systole (dotted line). TEE (Panel B): the AoA diameter is measured on the mid-esophageal 120° to 140° long-axis view on the left ventricular outflow tract at the point of insertion of the right and non-coronary aortic leaflet in mid-systole (dotted line). AoA: aortic annulus; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.

The MDCT exams were performed with a Discovery HD750 scanner (GE Healthcare, Milwaukee, WI). All patients with a resting heart rate≥70 beats/min received oral dose of ivabradine (10 mg/die) for 24 to 48 hours before MDCT to achieve a target heart rate<70 bpm. No patients were excluded because target heart rate was not reached.

The MDCT parameters were slice configuration 64 x 0.625 mm, gantry rotation time 350 ms, tube voltage 120 KVp and effective tube current 650 mA. All patients received a double-injection protocol of an 80-ml bolus of contrast (Iomeron 400 mg/ml, Bracco, Milan, Italy) through an antecubital vein at an infusion rate of 5 ml/s, followed by 50 ml of saline. The scan was performed as follows: after contrast enhancement reached a predefined threshold of 200 HU in the right ventricle, patients were instructed to hold a deep breath and the scan was started when a predefined threshold of 200 HU was achieved in the left atrium using retrospective ECG triggering.

AoA by MDCT was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets.[12] For each AoA, maximum diameter, minimum diameter and area were measured in systole in an orthogonal plane on the center line of the aorta.[1] (Figure 2). Aortic leaflet calcifications were assessed on a short-axis view and graded visually (grade 1: no calcifications, grade 2: mild calcifications, grade 3: moderate calcifications, grade 4: heavy calcifications) (13). Aortic leaflet length was defined as the distance from the basal attachment and the apex of the left coronary, right coronary and non-coronary leaflets.[1] (Figure 2).

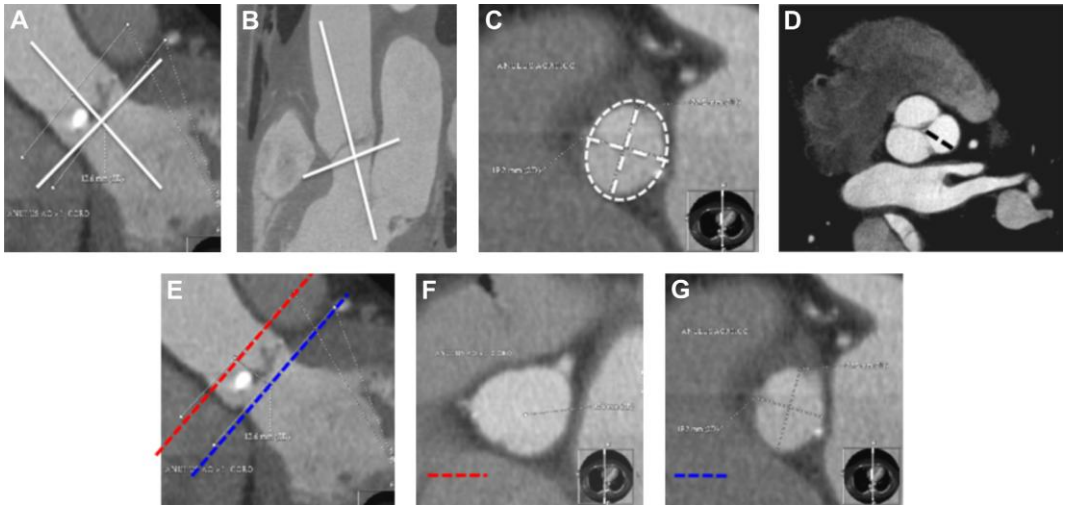

Figure 2. Methodology for assessing AoA size, aortic leaflet size and coronary artery ostia height using MDCT. Measurements of AoA (Panel A-C): AoA is defined as a virtual ring formed by joining the basal attachments of aortic valve leaflets. For each AoA, maximum diameter, minimum diameter and area (white dot line) were measured in an orthogonal plane on the center line of the aorta obtained in oblique-coronal and oblique-sagittal views, respectively. Measurement of leaflet size (Panel D): the distance between the basal attachment and the apex of the leaflets (black dot line) is determined. Measurement of coronary ostia height (Panel E-G): a coronal view of the ascending aorta (E) and two short axis at the level of the left main coronary ostium (red line) and AoA (blue line) are obtained. The distance between these two lines corresponds to the coronary ostium height. AoA: aortic annulus; MDCT: multidetector computed tomography.

The coronary ostia height was defined as the distance between 2 orthogonal planes on the center line of the aorta centered at the level of AoA and the ostium of the left main coronary artery and right coronary artery .[1] (Figure 2). For MDCT, the effective radiation dose was calculated as the dose-length product time a conversion coefficient for the chest (K= 0.017 mSv/mGy*cm).[14] Each MDCT variable was measured by an expert reader blinded to the other imaging modalities.

All patients were studied with a 1.5-T scanner (Discovery MR450, GE Healthcare, Milwaukee, WI) the same day of MDCT evaluation. Transaxial and coronal half-fourier acquisition single-shot turbo spin echo multislice pilot images were acquired during held expiration. Steady-state free precession cine acquisitions were then acquired, also during held expiration, without contrast agent injection due to the high contrast resolution between blood pool and cardiac chambers using the following parameters: echo time 1.57 ms, 15 segments, repetition time 46 ms without view sharing, slice thickness 8 mm, field of view 350 mm x 263 mm, and pixel size 1.4 mm x 2.2 mm. To acquire cine planes, multiple short axis and two-, three- and four-chamber long axis of left ventricle were reached according to guidelines.[15] Using long-axis plane of the left ventricle, two long-axis view of the aortic root and ascending aorta were obtained (Figure 3).

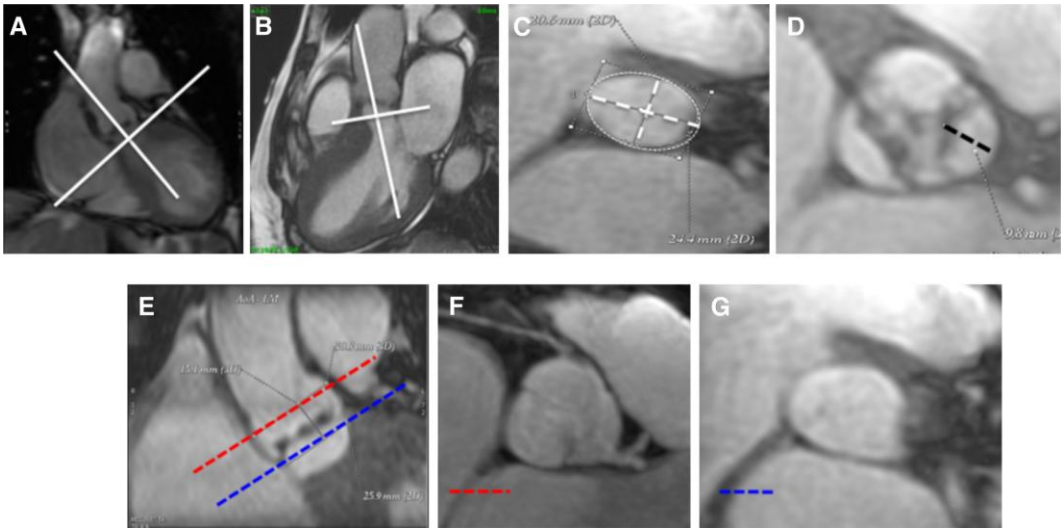

Figure 3. Methodology for assessing AoA size , aortic leaflet size and coronary artery ostia using CMR. Measurements of AoA (A to C): AoA is defined as a virtual ring formed by joining the basal attachments of aortic valve leaflets. For each AoA, maximum diameter, minimum diameter and area (white dot line) were measured in an orthogonal plane on the center line of the aorta obtained in oblique-coronal and oblique-sagittal views, respectively. Measurements of leaflet size (D): the distance between the basal attachment and the apex of the leaflets (black dot line) is determined. Measurement of coronary ostia height (E to G): a coronal view (E) and 2 short axis of the ascending aorta (F and G)at the level of the left main coronary ostium (red line) and AoA (blue line) are obtained. The distance between these two lines corresponds to the coronary ostium height.

Thus, serial short-axis cines orthogonal to the LVOT (3-mm thickness with 1.5-mm overlapping) were imaged including the entire aortic root (Figure 3).

AoA by CMR was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets. For each AoA, maximum diameter, minimum diameter and area were measured in systole in an orthogonal plane on the center line of the aorta (Figure 3). Aortic leaflet length and and coronary ostia height were measured as previously described for MDCT (Figure 3).

Each CMR variable was measured twice by one of the investigators (GP), while another blinded reader (DA) measured the same CMR variables once again to test intra-observer and inter-observer variability. All CMR readers were blinded to the other imaging modalities.

TAVI were performed in a hybrid operating room with general anesthesia, endotracheal intubation, and fast-track anesthesia protocol by a combined team of cardiologists, cardiac surgeons and anesthesiologists. The Sapien valve (Edwards Lifesciences Inc, Irvine, CA) in three different sizes (23-mm, 26-mm and 29-mm expanded diameter) was used in all patients. The final choice of prosthesis size and approaching modality were made according to guidelines.[16]

Statistical analysis was performed with the SPSS version 17.0 software (SPSS Inc., Chicago, Il). Continuous variables were expressed as mean±SD, and discrete variables as absolute numbers and percentages. The intra-observer and inter-observer variability for the evaluation of CMR variables was defined by the coefficient of variation. Student *t* test was used to test differences of continuous variables between the baseline and post-TAVI parameters. The Spearman's correlation and Bland-Altman analysis were used for comparing CMR to MDCT values. P value <0.05 was considered statistically significant.

Results

Clinical characteristics of the 50 patients included in the study are summarized in Table 1. All patients had severe aortic stenosis with normal left ventricle volumes and low-normal ejection fraction (Table 1). The overall effective radiation dose of MDCT was 15.4±5.3 mSv. The aortic root measurements by all imaging modalities and the differences between CMR versus other imaging modalities are reported in table 2 and 3, respectively. Both TTE and TEE showed a underestimation of the AoA area in comparison with CMR ($p<0.01$). On the contrary no differences were observed between CMR and MDCT except for aortic valve calcifications that have been underestimated by CMR ($p<0.05$). The inter-observer and intra-observer variability of CMR measurements is shown in Table 4.

Table 1. Clinical and echocardiographic characteristics of study population. Data are presented as mean±SD.

Variable	Baseline	After implantation
Clinical characteristics		
Number of patients, n	50	---
Gender (men/women), n	27/23	---
Age (yrs)	79.6±7.5	---
Body mass index (kg/m^2)	25.9±5.6	---
BSA (m^2)	1.8±0.2	---
Logistic EuroSCORE	22.4±8	---
TTE characteristics		
LV EDV /BSA (ml/m^2)	58.4±25.1	51.6±21.7
LV ESV /BSA (ml/m^2)	26.3±19.3	23.3±15.1
LV EF (%)	57.8±11.8	57.4±12.2
Mitral regurgitation (0-4)	1.0±0.8	1.0±0.7
Peak aortic gradient (mmHg)	78±18.5	19.3±6.9
Mean aortic gradient (mmHg)	47.8±12.2	10.8±5.0
Aortic valve area/BSA (cm^2/m^2)	0.4±0.1	1.4±0.4
Aortic regurgitation (0-4)	1.2±0.9	0.5±0.9
Pulmonary pressure (mmHg)	39.3±10.4	36.8±8.6
CMR characteristics		
LV EDV/BSA (ml/m^2)	85.7±29.3	---
LV ESV /BSA (ml/m^2)	46.1±41.6	---
LV EF (%)	55.3±13.9	---
RV EDV /BSA (ml/m^2)	65.5±15.9	---
RV ESV /BSA (ml/m^2)	24.6±10.7	---
RV EF (%)	63±10.3	---
Mitral regurgitation (ml)	3.4±6.9	---
Aortic valve area/BSA (cm^2/m^2)	0.4±0.1	---
Aortic regurgitation (ml)	4.2±8.0	---

Values expressed as mean Values espressed as mean±SD.

With regard to AoA maximum diameter, minimum diameter and area, TTE (Figure 4) and TEE (Figure 5) showed only a moderate agreement versus CMR as showed by Pearson's correlation and Bland-Altman analysis, respectively. On the contrary, CMR showed an excellent agreement with MDCT regarding to AoA root geometry (Figure 6), heights of aortic cups (Figure 7) and distance between AoA and coronary artery ostia (Figure 8).

Table 2. Aortic root measurements.

Variable	CMR	TTE	TEE	MDCT
AoA maximum diameter (mm)	26.4±2.8			26.5±2.8
AoA minimum diameter (mm)	20.6±2.3	21.9±2.4	22.6±2.6	20.2±2.2
AoA area (mm^2)	450±86	380±82	404±90	445±85
Aortic valve calcification (1-4)	2.9±0.8			3.4±0.7
Lenght of the left coronary leaflet (mm)	13.9±2.2			14±2.3
Lenght of the right coronary leaflet (mm)	13.3±2.1			13.3±2.3
Lenght of the non coronary leaflet (mm)	13.4±1.8			13.4±2.0
AoA-to-left coronary ostium distance (mm)	16.1±2.8			16.2±3.1
AoA-to-right coronary ostium distance (mm)	16.1±4.4			16.0±4.3

Values expressed as mean Values espressed as mean±SD.

Table 3. Differences of aortic root measurements betweeen cardiac magnetic resonance (CMR) and other imaging methods.

Variable	CMR vs TTE	CMR vs TEE	CMR vs MDCT
AoA maximum diameter (mm)	5.1±2.8*	4.3±2.6†	0±0.8
AoA minimum diameter (mm)	-0.9±2.2*	-1.6±2†	0.4±1
AoA area (mm^2)	70.2±82.1*	44.9±76.1†	4.9±21.2
Aortic valve calcification (1-4)			-0.4±0.2§
Lenght of the left coronary leaflet (mm)			-0.1±0.5
Lenght of the right coronary leaflet (mm)			0±0.7
Lenght of the non coronary leaflet (mm)			0.1±0.6
AoA-to-left coronary ostium distance (mm)			-0.1±1.1
AoA-to-right coronary ostium distance (mm)			0.1±1.1

Data are presented as mean±SD; *: p <0.01 for CMR versus TTE; †: p <0.01 for CMR versus TEE; §: p <0.05 for CMR versus MDCT

Table 4. Intra- and inter-observer variability of cardiac magnetic resonance measurements.

Variable	Intraobserver CV (%)	Interobserver CV (%)
AoA maximum diameter	1.4	2.1
AoA minimum diameter	1.2	2.0
AoA area	1.4	2.0
Aortic valve calcification	2.8	3.9
Lenght of the left coronary leaflet	2.0	2.3
Lenght of the right coronary leaflet	2.1	2.5
Lenght of the non coronary leaflet	2.0	2.4
AoA-to-left coronary ostium distance	2.5	3.1
AoA-to-right coronary ostium distance	2.4	3.0

Values shown are coefficients of variation (CV) expressed as percentages.

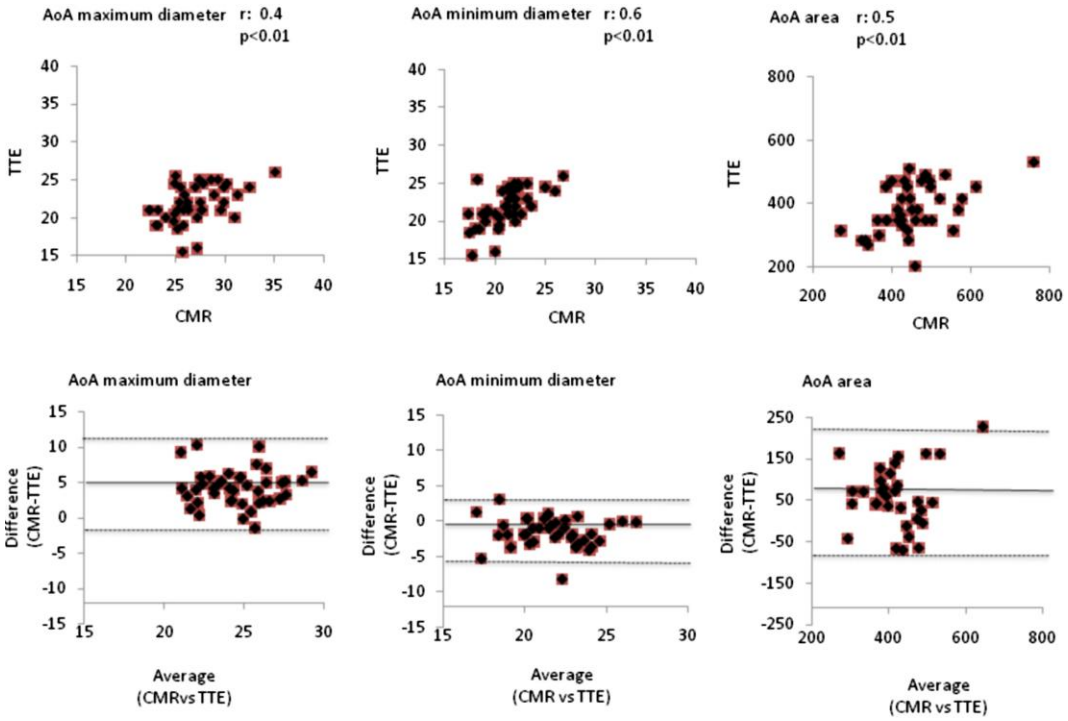

Figure 4. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between CMR and TTE assessment of AoA maximum diameter, minimum diameter and area. AoA: aortic annulus; CMR: cardiac magnetic resonance; TTE: transthoracic echocardiography.

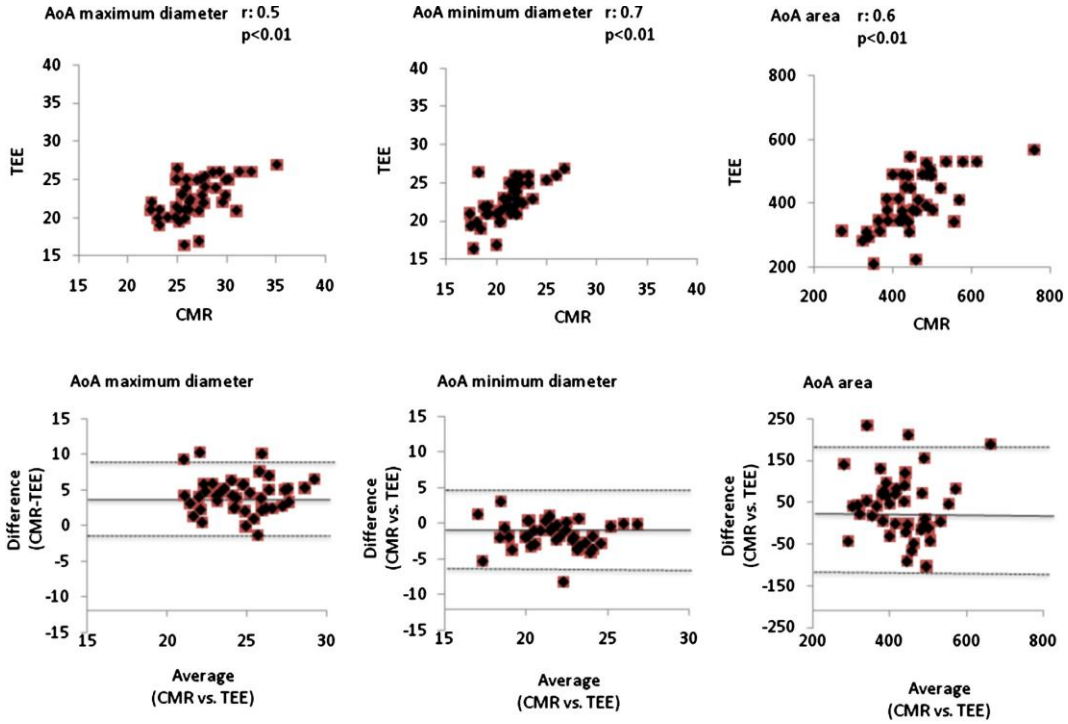

Figure 5. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between CMR and TEE assessment of AoA maximum diameter, minimum diameter and area. AoA: aortic annulus; CMR: cardiac magnetic resonance; TEE: transesophageal echocardiography.

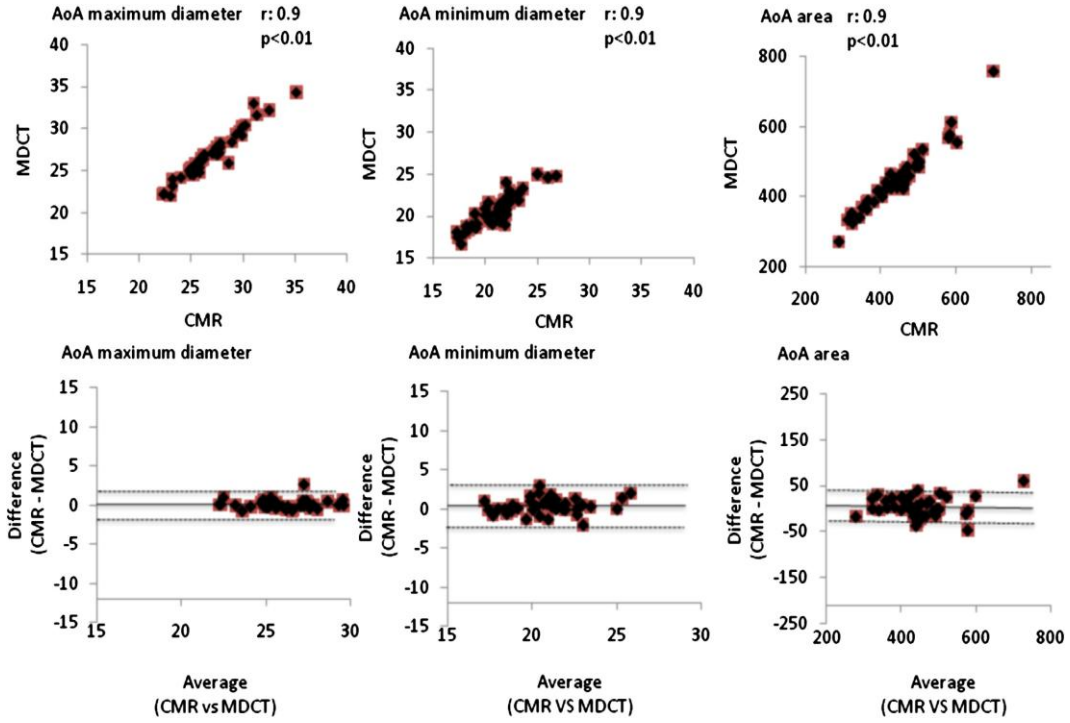

Figure 6. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between CMR and MDCT assessment of AoA maximum diameter, minimum diameter and area. AoA: aortic annulus; CMR: cardiac magnetic resonance; MDCT: multidetector computed tomography.

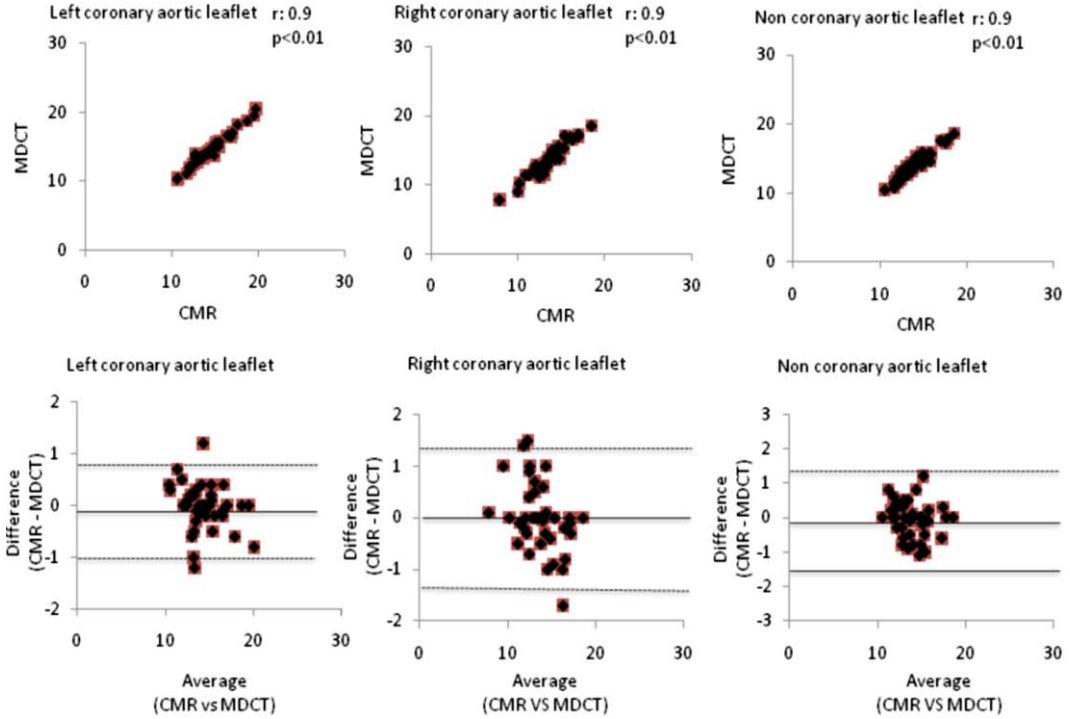

Figure 7. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between CMR and MDCT assessment of left coronary, right coronary and non coronary aortic leaflets. CMR: cardiac magnetic resonance; MDCT: multidetector computed tomography.

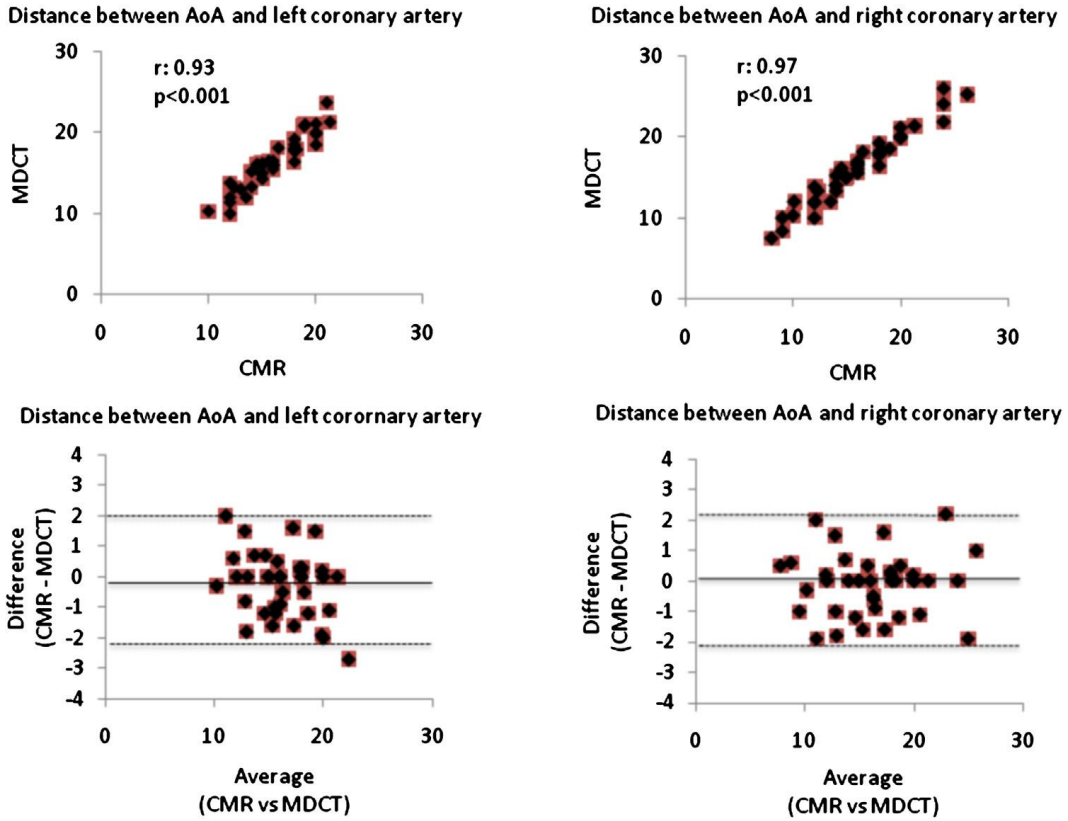

Figure 8. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between CMR and MDCT assessment of the distance between aortic annulus (AoA) and left main coronary artery and right coronary artery ostia.

According to AoA area measured by MDCT (2), in 2 patients both TTE and TEE suggested to not perform TAVI for too small AoA size despite a 23-mm prosthesis was implanted based on MDCT measurements without complications. In other 2 patients TAVI was not performed because MDCT showed a too large AoA while both TTE and TEE suggested a 29-mm valve. In the remaining patients, TTE and TEE suggested a smaller, equal or larger prosthesis in 14 (28%), 31 (62%), 1 patients (2%) and in 8 (16%), 34 (68%), 4 patients (8%), respectively. CMR suggested a smaller, equal or larger prosthesis in 1 (2%), 44 (88%) and 2 patients (4%) and agree with MDCT to not perform TAVI for too large AoA size in 1 patient (2%). Finally, in 1 patients (2%) CMR suggested to not perform TAVI for too large AoA size despite a 29-mm prosthesis was implanted based on MDCT measurements without complications and in 1 patients (2%) TAVI was not performed because MDCT showed a too large AoA while CMR indicated a 29-mm valve. Therefore the agreement to perform the procedure and the agreement for prosthesis size between TTE, TEE and CMR vs MDCT were 92% and 62%, 92% and 68%, 96% and 88%, respectively.

Discussion

Accumulating data have reported promising results concerning procedural success, quality of life improvement, and short-, mid- and more recently long-term outcomes after TAVI in high-risk patients with severe aortic stenosis. Nevertheless, among clinically relevant complications of TAVI aortic regurgitation following valve implantation, which is mainly of paravalvular origin, has been shown to occur in a sizable proportion of patients and it is associated with a five-fold increase of one-year mortality after the procedure. [17-19] Moreover, coronary artery occlusion has been reported to occur during TAVI. [20] Development of these serious complications depends on several factors that are in connection with aortic root anatomy and its relation to the implanted prosthesis. They include AoA shape and size, degree of annular and leaflet calcifications [21], left ventricle outflow tract anatomy, prosthesis/annulus incongruence [2,21,22], incorrect valve positioning [17, 18] and low take-off of coronary ostia with excessively enlarged valve leaflets. [17,18] Therefore, accurate evaluation of aortic root morphology and dimensions prior to TAVI integrating different non-invasive imaging modalities may reduce the chance for error and may prevent these complications.

To the best of our knowledge, this is the first study showing that a comprehensive evaluation with CMR of aortic root including measurement of AoA size, aortic leaflet dimensions, and height of coronary artery ostia is feasible and accurate. Echocardiography has been commonly used for pre-procedural assessment and has the advantage of providing physiologic data. However, there is growing evidence that 2D evaluation of the aortic root fails to appreciate its non-symmetric and complex geometry, while 3D imaging as can be performed with MDCT provides a more comprehensive and accurate morphologic and dimensional assessment. [1-5] Unfortunately, up to 20% of patients undergoing TAVI cannot be studied with MDCT.[1]

Our study shows that 3D evaluation of the aortic root with CMR not only is feasible and accurate but may also circumvent some of the inherent limitations of MDCT. Indeed, compared to MDCT no contrast agent administration and radiation exposure is needed with CMR, while heart rate control is not a major issue due to a better temporal resolution of the latter technology that, unlike MDCT, does not loose image quality and accuracy with higher heart rate. [23] Tsang et al. [8] have demonstrated that CMR measurements of AoA are the most accurate in comparison with 3D-echocardiography and MDCT in 28 explanted human hearts. Burman et al. [9] studied 120 healthy volunteers with 1.5-T CMR. They utilized steady-state free precession cine acquisition aligned with the left ventricle outflow tract in oblique long-axis sagittal and coronal orientations, and defined AoA as the two diameters that transacted the aortic root at its widest point. Similarly, Jabbour et al. [10]

studied 202 consecutive patients referred for TAVI with the same imaging technology demonstrating that CMR provides highly reproducible information for the assessment of these patients and for the prediction of post-procedure paravalvular aortic regurgitation. However, in both studies AoA was measured in a long-axis view as the distance between the basal attachments of the aortic cusps. This approach may underestimate true AoA size because it cuts a tangent across the root in a higher position as compared to the true basal ring. [12] Indeed, several studies demonstrated that a cross-sectional measurement of the AoA is superior to conventional oblique coronal and sagittal planes sizing. [5] Our study indicates that CMR allows accurate short-axis visualization of the AoA and precise measurement of the virtual ring corresponding to the site of prosthesis deployment with high reproducibility and accuracy as compared to MDCT.

Previous reports showed that assessment of coronary ostia height and aortic valve leaflet dimensions is a key step for patient selection and procedural planning in order to prevent coronary obstruction during TAVI. Although rare, this is a life-threatening complication that has been associated with a short distance between AoA and coronary ostia and excessively enlarged aortic valve leaflets (24). Our study shows that CMR can provide accurate estimation of both variables with good reproducibility, as demonstrated by a very low inter-observer and intra-observer variability.

An intrinsic shortcoming of CMR is reduced visualization of calcium burden and this is confirmed in our study by the lower score of aortic leaflet calcifications observed with CMR as compared to MDCT. However, despite aortic valve calcification has been demonstrated to be a predictor of post-procedure paravalvular regurgitation, precise calcium estimation does not have a key role in patient selection and TAVI planning.

An emerging issue in patients undergoing TAVI is acute kidney injury. Indeed, a recent meta-analysis reports a 20.4% pooled estimate rate of renal insufficiency after TAVI and worsening of renal function has been demonstrated to be a strong predictor of mortality (25, 26). This complication is likely multifactorial.[25,26] However, pre-procedural aortic root evaluation with CMR without i.v. gadolinium injection has the advantage of reducing the total amount of contrast agent decreasing the risk of nephrotoxicity.

Finally, in our study the overall radiation exposure of MDCT was 15.42 mSv, a value that is higher than the 10 mSv cut-off value suggested by the American Heart Association. Although the use of prospective ECG-triggering instead of retrospective ECG-triggering should allow a significant reduction of effective radiation exposure during MDCT [27], this is not applicable in patients with heart rate>65 bpm [27] due to the presence of misalignment artefacts. These patients are common in population with aortic stenoses such as in our study. Moreover, a scan covering the entire cardiac

cycle is mandatory due to the different measurements of AoA between systole and diastole. [28] This is only possible by using the retrospective ECG-triggering. However, although the high radiation exposure may be a minor hazard in an elderly population, future technology developments and increased clinical experience will likely allow to offer TAVI even to younger patients in whom an imaging modality without ionizing radiation such as CMR may be of significant value.

A number of limitations of this study should be addressed. First, this is a single-center study that enrolled a relatively small number of patients. However, the strong correlation observed between CMR and MDCT suggests that the level of accuracy demonstrated by CMR could be replicated also in a larger patient population. Second, our measurements apply to the balloon-expandable Sapien valve that was the only prosthesis used in this study. Third, CMR accuracy was not assessed against a true gold standard. However, correlation between different imaging modalities is still an issue of debate and MDCT evaluation has demonstrated to predict important clinical end points such as post-procedure PAR. Fourth, also CMR could not be performed in a subgroup of patients.

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Chapter 3

Feasibility and accuracy of 3DTEE versus CT for the evaluation of aortic valve annulus to left main ostium distance before transcatheter aortic valve implantation.

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Abstract

Objectives. The aims of this study were to analyze in a large series of patients undergoing transcatheter aortic valve implantation (TAVI): 1) the accuracy of 3-dimensional transesophageal echocardiographic (3DTEE) measurement of left coronary cusp (LCC) length and of the distances from left main coronary ostium (LM) to the aortic annulus (AoA) pre-operatively and to the aortic prosthesis post-operatively; and 2) the role of the 3DTEE measurements in predicting the prosthetic deployment and the association between prosthesis position and aortic regurgitation (AR) and/or prosthesis-patient mismatch (PPM).

Background. Coronary ostia occlusion is a possible complication in TAVI; therefore, the careful pre-operative evaluation of AoA-LM and LCC length, and the post-operative analysis of the relationship between the prosthesis and LM, may influence the procedural outcomes. Even though multidetector computed tomography (MDCT) is the gold standard pre-operatively, sometimes it cannot be performed

and it is rarely repeated post-operatively.

Methods. In 122 patients undergoing TAVI, pre-operative AoA-LM and LCC measurements obtained by 3DTEE and MDCT were compared. Post-operatively, the feasibility of 3DTEE evaluation of the prosthesis-LM distance was performed. The relationship between 3DTEE overlap of the prosthesis with the anterior mitral leaflet and AR/PPM was assessed.

Results. Pre-operatively, 3DTEE AoA-LM ($r = 0.83$) and LCC ($r = 0.69$) significantly correlated with MDCT. Post-operatively, 3DTEE prosthesis-LM distance was 2.1±1.9 mm. The prosthesis reached or exceeded LM in 6 and 10 cases, respectively. Prosthesis overlap with mitral leaflet was 4.7±1.8 mm. Significant correlation between the 3DTEE computed and nominal length of the prosthesis was found ($r = 0.61$). No correlations were found between prosthesis–mitral leaflet overlap and aortic regurgitation or PPM.

Conclusions. AoA-LM distance and LCC length may be accurately estimated by 3DTEE, which may represent a valid alternative to MDCT. Pre- and post-3DTEE data concerning the aortic root, such as LM, aortic valve, and prosthetic morphology, give new insights into TAVI and its complications.

Introduction

Transcatheter aortic valve replacement (TAVI) has become a valid alternative to conventional surgery in selected high-risk patients with severe and symptomatic aortic valve stenosis. [1,2] One of the major complications reported after TAVI is coronary ostia impairment [3-7] due to the presence of low coronary ostia and/or the occluding effect of aortic leaflets displacement by prosthetic percutaneous implantation.

Therefore a careful preoperative evaluation of the distance between aortic annulus (AoA) and left main coronary ostium (LM) and of left coronary cusp (LCC) is necessary and an accurate analysis of the critical relationship between the prosthesis and LM postoperatively should be performed.

Preoperatively AoA-LM distance and LCC length estimation are generally obtained through multidetector computed tomography (MDCT) which is the gold standard in this context, allowing an accurate assessment of aortic root geometry. [7-9] Unfortunately MDCT cannot be performed in arrhythmic patients or in cases with severe impaired renal function and it is rarely repeated postoperatively for clinical reasons. Moreover immediate post-procedural imaging inside the operatory theatre is possible only by using echocardiography or angiographic techniques.

Three-dimensional transesophageal echocardiography (3DTEE) has been demonstrated very useful in the management of TAVI in preoperative evaluation of AoA dimensions [8,10] and may be used as substitute for MDCT in AoA measurement. The incremental value of its application in procedural monitoring of TAVI and of post-procedural result assessment is also well known. [11,12] Moreover few data are available concerning the immediate postoperative relationship between the device and coronary ostia.

Our aims were to study in a large series of patients: 1) the feasibility of preoperative AoA-LM distance and LCC length measurements by 3DTEE; 2) its accuracy in comparison with MDCT-derived measurements; 3) the feasibility of postoperative 3DTEE evaluation of the distance between the prosthesis and LM; 4) the accuracy of the 3DTEE-derived measurements in predicting the stent landing zone as defined by the overlap of the prosthesis with mitral leaflet; and 5) the association between prosthesis deployment and regurgitation, positioning and spatial relation with LM.

Methods

Study population

From January 2008 to June 2011, 276 consecutive patients underwent TAVI using the Edwards Sapien prosthesis in Centro Cardiologico Monzino IRCCS.

In all patients a transthoracic echocardiography was performed before surgery to confirm the severity of the aortic valve stenosis (mean trans-aortic pressure gradient ≥40 mmHg or an aortic valve area <1 cm^2) [13] and to assess the feasibility of the percutaneous procedure (absence of aortic bicuspid valve, aortic annulus dimensions between >18mm and 26mm). [12,14] Before hospital discharge, after TAVI procedure, transthoracic echocardiography was repeated and the effective orifice area of the prosthesis was obtained using the continuity equation approach and indexed to body surface area. Prosthesis–patient mismatch (PPM) was defined in presence of orifice area ≤ 0.85 cm^2/m^2. [15-17]

Before TAVI procedure, an invasive coronary and peripheral vascular angiography was performed according to guidelines [14] in order to rule out coronary and peripheral disease. In 190 out of 276 patients, a MDCT exam was performed. In 268 patients, peri-procedural 2-dimensional TEE monitoring, completed with 3DTEE acquisitions, was performed. Exclusion criteria were: atrial fibrillation or other arrhythmias, impaired renal function, inability to sustain a 10 second breath-hold, presence of esophageal diseases or clinical contraindication to general anaesthesia during the procedure, stenosis of the left main and/or the proximal descending coronary artery. Therefore 122 out of 276 patients were enrolled in this study.

The study protocol was approved by the ethics committee and, prior to participation, informed consent was obtained from all patients.

Transesophageal echocardiography

Patients were imaged during TAVI procedure using a commercially available echocardiographic system (iE33, Philips Medical System, Andover, MA) equipped with a X7-2t probe, allowing 2D multiplane, real-time 3D and full volume TEE acquisitions. Image acquisition was performed by an experienced cardiologist. Preoperatively accordingly to the current clinical practice, a 2-dimensional TEE acquisition in zoom mode of the left ventricular outflow tract from the mid-esophageal position with scanning planes from 115° to 160° was performed in all patients in order to assess precise measurements of AoA and aortic root. Moreover, real-time zoomed 3D or full volume images containing the whole aortic apparatus and the proximal ascending aorta were acquired both pre- and post-TAVI for quantitative analysis performed with a commercially available software package (3DQ,

Q-Lab Version 7.0, Philips Medical Systems). Briefly, before TAVI the 3D dataset was analyzed moving 3 different orthogonal cut planes: the first cut plane was transversal, oriented to visualize a short-axis view of the aortic annulus and on this plane the maximum diameter (Max-D), the minimum diameter (Min-D) and the area of AoA were measured. The second and the third were both longitudinal planes, one adjusted orthogonal to the short-axis in order to obtain a sagittal view of the ascending aorta. The other longitudinal plane was gradually rotated until the LM ostium appeared allowing the measurement of AoA-LM distance (Figure 1).

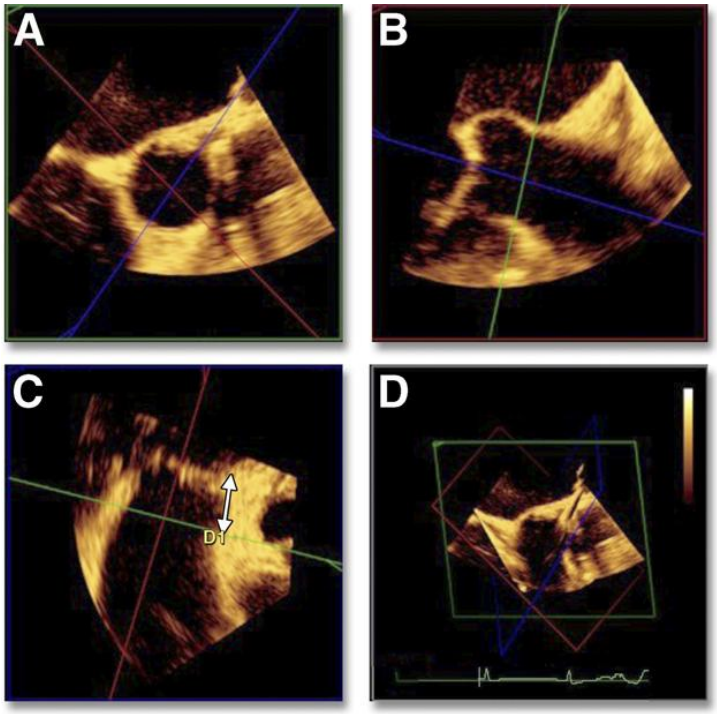

Figure 1. AA-LM distance measured by 3DTEE. Example of 3-dimensional (3D) transesophageal (TEE) measurement of the distance between aortic annulus (AA) and left main coronary ostium (LM). The 3D dataset was analyzed through 3 different orthogonal cut planes: green plane (A) is a short axis view of aortic root crossing the LM; red (B) and blue (C) planes are sagittal views of the ascending aorta. The blue plane was gradually rotated until the LM appeared allowing the measurement of the distance between AA and LM ostium (white arrow). (D) The position and the relationship of each plane in the 3D dataset are shown.

In addition, in the same plane, LCC length was assessed as the distance between the tip of the leaflet and the AoA (Figure 2).

In the post-TAVI 3D dataset we evaluated: 1) L_1 = the overlap of the prosthesis with the anterior mitral valve leaflet, defined as the distance between the ventricular edge of the aortic

prosthesis and the native AoA; 2) L_2 = the distance between the distal edge of the prosthesis and LM ostium.

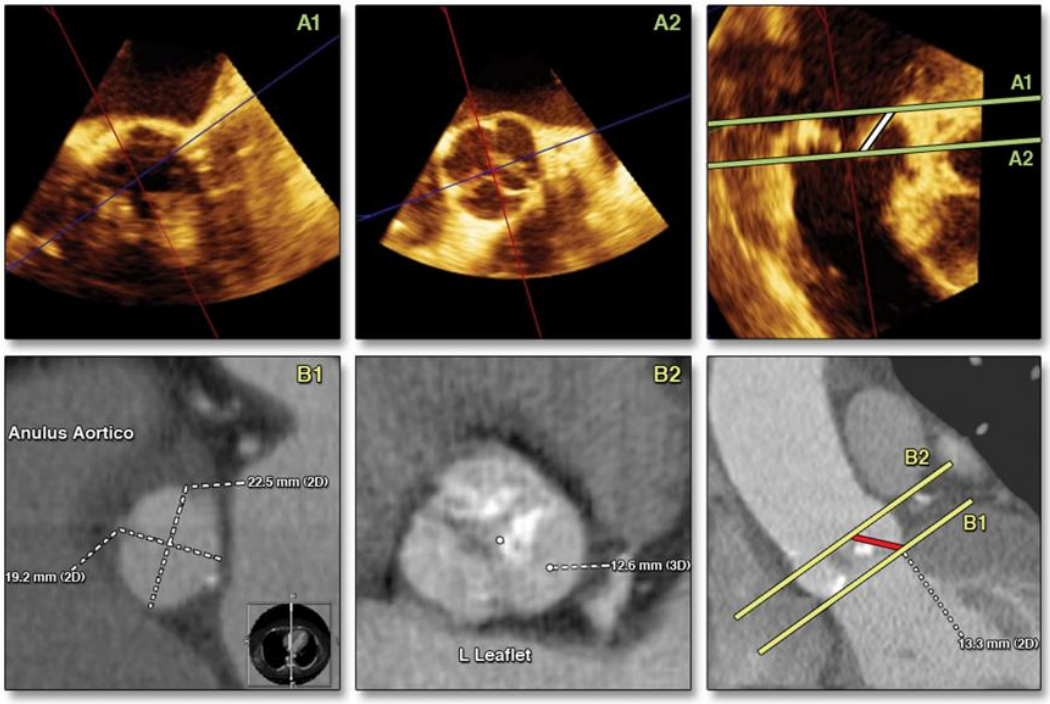

Figure 2. LCC Length Measured by 3DTEE and MDCT. (Top) Example of 3DTEE measurement of the left coronary cusp (LCC) length. A short-axis view (A1) at the level of AA (top, left); a shortaxis view (A2) at the level of the tip of the leaflets (top, middle); a sagittal view of the ascending aorta with the LCC length (white line) measured as the distance between plane A1 and A2 (top, right). (Bottom) Example of multidetector computed tomography (MDCT) measurement of the LCC length. A short-axis view (B1) at the level of AA (bottom, left); a short-axis view (B2) at the level of the tip of the leaflets (bottom, middle); a sagittal view of the ascending aorta, with the LCC length (red line) measured as the distance between plane B1 and B2 (bottom, right). Abbreviations as in Figure 1.

The 3DTEE prosthesis length was calculated as [(AoA-LM distance + L_1) - L_2] and this computed measurement was compared with the nominal prosthesis length (14mm, 17mm an 19mm for a 23mm, 26mm and 29mm device, respectively) (Figure 3).

A 3D dataset was considered unsuitable for analysis if it contained artifacts or if LM ostium was not clearly visible for artifacts or poor quality of the image.

Finally after the device deployment and after removal of the catheters the presence of post-procedural paravalvular aortic regurgitation (AR) was evaluated. Post-procedural AR was quantified according to standard echocardiographic color-Doppler method using the jet width and extension and graded as: 0 (absent), 1 (mild), 2 (mild to moderate), 3 (moderate to severe), 4 (severe). Paravalvular AR was considered significant if greater than or equal to 2.

Figure 3. Post-Operative 3DTEE Evaluation. Example of a 3DTEE post-operative evaluation of the aortic root and prosthesis. Three different orthogonal views are shown: (left) a short-axis view of aortic root at the level of the aortic prosthesis and the LM; (middle) a longitudinal view of the ascending aorta showing the aortic prosthesis length and the overlap of the prosthesis with the anterior mitral valve leaflet; and (right) a longitudinal view of the ascending aorta crossing the LM; this view allows the measurement of the distance between the upper edge of the prosthesis and the LM. Abbreviations as in Figure 1.

Multidetector computed tomography

All examinations were performed with a LightSpeed VCT XT Scanner (GE Healthcare, Milwaukee, Wisconsin). Scanning parameters were slice configuration 64 x 0.625mm, gantry rotation time 350 ms, tube voltage 120 kVp, and effective tube current 650 mA. Contrast enhancement was achieved with a tri-phasic injection of 80 mL bolus of Iomeron 400 mg/mL (Bracco, Milan, Italy) through an antecubital vein at a 5 mL/s infusion rate, followed by 50 mL of saline solution and a further 50 mL bolus of contrast at 3.5 mL/s. After the threshold level of 200 Hounsfield units (HU) in the right ventricle was achieved, patients were instructed to hold a deep breath, and the scan was started when a threshold of 200 HU was reached in the left atrium allowing the synchronization of the arrival of the contrast media and the scan. Data acquisition was performed with retrospective ECG-triggering.

Image analysis was performed on a separate computer workstation. AoA was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets. [18] Max-D, Min-D and the area of AoA were measured in an orthogonal plane on the center line of the aorta in systole. The distance between the AoA and the LM was defined as the distance between the short axis at the level of the LM and the short axis at the level of AoA (Figure 4). LCC length was defined as the distance between 2 orthogonal planes on the center line of the aorta, centered at the basal attachment and apex of the LCC in end-diastolic phase (Figure 3).

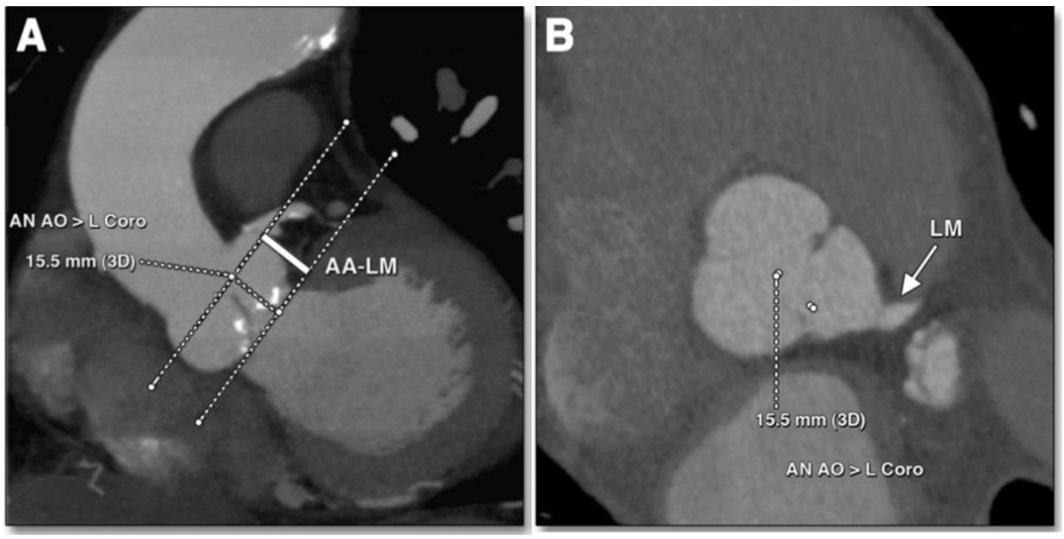

Figure 4. AA-LM Distance Measured by MDCT Example of MDCT measurement of AA to LM distance. (A) A sagittal view of the ascending aorta; AA-LM was measured as the distance between the short axis at the level of the LM and the short axis at the level of the AA. (B) A short-axis view at the level of the LM. AN AO = aortic annulus; L Coro = left coronary artery; other abbreviations as in Figures 1 and 2.

Statistical analysis

Data are presented as mean and standard deviation for continuous variables, while frequencies and relevant percentages for categorical variables. Linear regression analysis with Pearson's correlation coefficient was used to evaluate the relationship between computed and nominal prosthesis length, LCC length and AoA-LM distance, and between 3DTEE and MDCT measurements. Also, Bland-Altman analysis was used to assess the inter-technique agreement by calculating the bias (mean difference) and the 95% limits of agreement (defined as 1.96SD around the mean difference). A Chi-Square test was performed to investigate the association between prosthesis-mitral leaflet overlap, the entity of paravalvular AR and the presence of PPM. To determine the reproducibility of the AoA-LM distance, intra- and inter-observer variability were assessed in a subset of 30 patients as coefficient of variation, defined as the ratio between the standard deviation and the mean of the 2 measurements, expressed as a percentage. During these repeated analyses, investigators were blinded to each other's and prior measurements. A Bland-Altman analysis was performed to evaluate the concordance between the 2 observers and between the first observer and himself. All statistical analysis were performed using SPSS 17.0 (SPSS Inc., Chicago, IL).

Results

All patients underwent to TAVI with a balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) through trans-apical (43 pts) or trans-femoral (79 pts) approach. The procedures were performed under general anesthesia with TEE and fluoroscopic guidance. A 23 mm, 26 mm and 29 mm prosthesis were implanted in 58, 59 and 5 patients, respectively. Clinical baseline characteristics of the study population are reported in Table 1.

Table 1. Baseline clinical and 2D echocardiographic characteristics of the study population.

Clinical and echocardiographic parameter	
Age, yrs	81±7
Male/female	39/80
Body surface area (m^2)	1.7±0.2
Logistic EuroSCORE (%)	19±11
NYHA functional class, %	
I	0 (0)
II	38 (32)
III	61 (51)
IV	20 (17)
Left ventricular ejection fraction, %	58±12
Aortic valve area, cm^2	0.65±0.16
Aortic annulus, mm	21±2
Left ventricular outflow tract, mm	20±2
Sinus of Valsalva, mm	31±4
Sinotubular junction, mm	27±4
Mean transaortic pressure gradient, mmHg	52±15

Values are mean±SD;, n/n, or n(%). EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart association; 2D = 2-dimensional

Paravalvular AR immediately post-TAVI was graded: 0 in 54 patients (44%), 1 in 52 patients (43%), 2 in 14 patients (11%), 3 in 1 patients (1%) and 4 in 1 patient (1%). Therefore, AR was greater than or equal to 2 in 16 patients (13%). The incidence of PPM post-TAVI was 45% (55 patients), as assessed by transthoracic echocardiography before hospital discharge.

The measure of AoA-LM distance was feasible in 119 of 122 patients (97.5%) with a 3DTEE acquisition focused on the aortic apparatus and in all the patients with MDCT. Three-dimensional TEE estimation of the distance between LM and the prosthesis was feasible in 110 cases (90%).

Table 2 shows mean values of the AoA-LM distance, LCC length, Min-D, Max-D and Area of AoA obtained by 3DTEE and MDCT for all patients and separately for each size of prosthesis implanted.

Table 2. Correlations between 3DTEE and MDCT measurements.

All sizes	3DTEE	MDTC	r	p value
AoA-LM [mm]	13.5±2.2	13.9±2.2	0.83	<0.001
LCC Length [mm]	13.7±1.8	13.6±1.8	0.69	<0.001
Min-D [mm]	21.3±2.1	21.4±2.2	0.70	<0.001
Max-D [mm]	24.6±2.3	25.3±2.2	0.68	<0.001
Area [cm^2]	4.1±0.7	4.3±0.8	0.76	<0.001
Size 23 (n=57)	**3DTEE**	**MDTC**	**r**	**p value**
AoA-LM [mm]	12.9±1.6	13.5±1.9	0.77	<0.001
LCC Length [mm]	13.1±1.8	12.9±1.7	0.60	<0.001
Min-D [mm]	19.9±1.4	19.9±1.4	0.44	0.002
Max-D [mm]	23.1±1.6	23.9±1.4	0.45	0.001
Area [cm^2]	3.6±0.4	3.7±0.4	0.51	<0.001
Size 26 (n=57)	**3DTEE**	**MDTC**	**r**	**p value**
AoA-LM [mm]	13.9±2.2	14.1±2.3	0.82	<0.001
LCC Length [mm]	14.2±1.6	14.1±1.7	0.73	<0.001
Min-D [mm]	22.5±1.7	22.7±1.6	0.47	0.01
Max-D [mm]	25.7±1.8	26.2±1.7	0.49	<0.001
Area [cm^2]	4.5±0.6	4.7±0.6	0.32	0.03
Size 29 (n=5)	**3D TEE**	**MDTC**	**r**	**p value**
AoA-LM [mm]	16.2±3.2	16.2±3.5	0.99	<0.001
LCC Length [mm]	15.4±1.3	14.5±1.9	0.58	0.31
Min-D [mm]	24.0±1.1	25.1±1.3	0.82	0.09
Max-D [mm]	28.3±2.2	30.0±0.9	-0.38	0.54
Area [cm^2]	5.4±0.6	5.9±0.4	0.37	0.54

Values are mean±SD. AoA-LM= distance between aortic annulus and left main coronary ostium; Area aortic annulus area; LCC length= distance between the tip of the left leaflet and the aortic annulus; Max-D and Min-D=maximum and minimum aortic annulus diameters; MDCT=multidetector computed tomography; 3DTEE= 3-dimensional transesophageal echocardiography.

All measurements were significantly correlated as depicted in the scatterplots of Figure 5 together with the results of Bland-Altman analysis showing a good agreement between the two techniques with a minimal underestimation of 3DTEE measurements compared with MDCT.

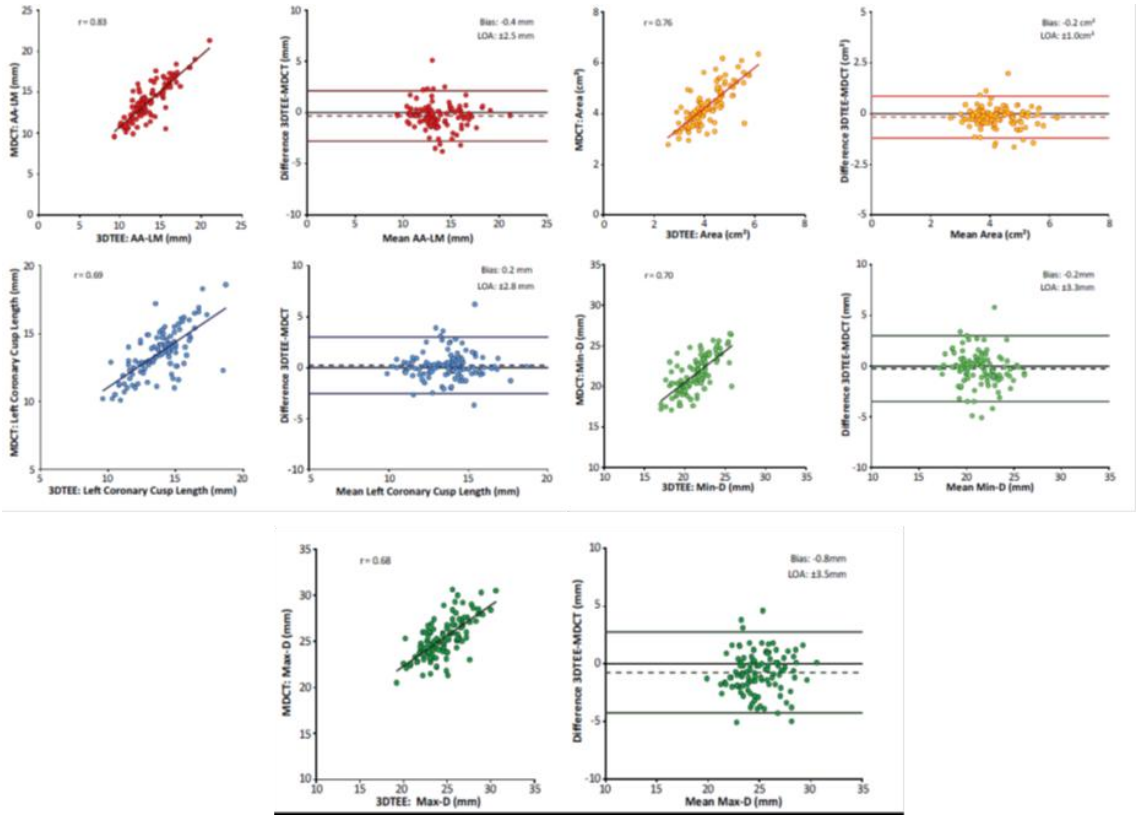

Figure 5. 3DTEE and MDCT correlations and agreements. Results of linear regression (left) and Bland-Altman analysis (right) for AoA-LM distance, LCC length, AoA area, minimum (min-D) and maximum (max-D) diameters, measured by 3DTEE and MDCT. Abbreviations as in Figure 1 and 2.

Three-dimensional TEE measurements of AoA-LM distance were found to be highly reproducible on both intra-observer and inter-observer variability analysis as depicted by lower coefficients of variation, 2.1% and 2.6% respectively. Figure 6 shows the results of Bland-Altman analysis of the agreement between repeated measurements of AoA-LM distance together with relevant bias and limits of agreement.

The mean value of overlap with the anterior mitral valve leaflet (L_1) was 4.5±1.9mm (range: -2.0-9.5mm) and the distance between the distal edge of the prosthesis and the left main coronary artery ostium (L_2) was 2.1±1.9mm (range: -2.0-6.5mm). The upper edge of the prosthesis reached (6 cases) or overlapped (10 cases) LM ostium.

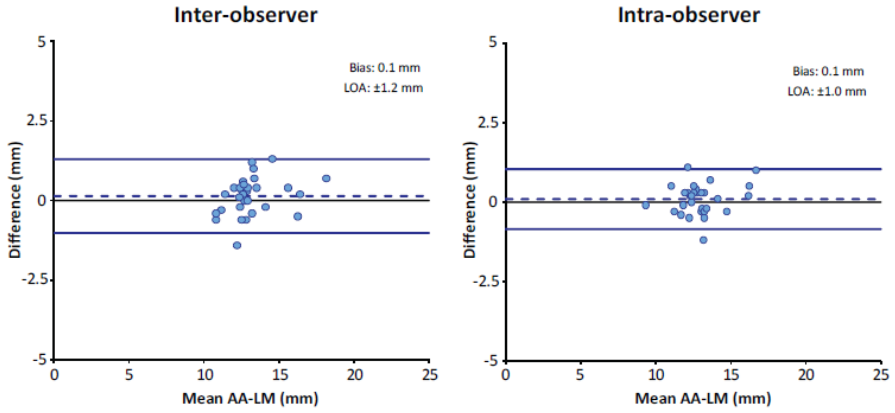

Figure 6. Interobserver and intraobserver variability. Results of Bland-Altman analysis of the agreement between repeated 3DTEE measurements of the distance between aortic annulus and left main (AA-LM) for interobserver (left) and intraobserver (right) variability obtained in a subset of 30 randomly selected patients.

Table 3 shows 3DTEE derived anatomical data regarding AoA-LM distance (preoperatively) and the characteristic of the prosthesis implantation (postoperatively) in each of these 16 cases.

Table 3. Pre- and post-operative 3DTEE measurements in each of the 16 cases in which the upper edge of the aortic prosthesis reached or overlapped LM ostium.

N°	3DTEE AoA-LM distance	3DTEE PR-LM distance	PR-anterior mitral leaflet overlap	PR size	Nominal PR length	Computed PR length
1	12.8	0	2.0	23	14	14.8
2	12.3	0	3.0	23	14	15.3
3	12.4	0	5.4	26	17	17.3
4	11.7	0	3.0	23	14	14.7
5	12.2	0	4.6	26	17	16.8
6	11.4	0	6.0	26	17	17.4
7	11.2	-1.0	3.7	23	14	14.8
8	15.6	-1.0	3.0	29	19	19.8
9	15.0	-1.0	2.0	23	14	15.4
10	14.8	-1.5	1.0	23	14	16.5
11	12.8	-1.6	1.8	23	14	15.9
12	10.7	-1.6	4.0	26	17	16.4
13	11.3	-2.0	4.0	26	17	17.0
14	9.3	-2.0	3.0	23	14	14.3
15	10.7	-2.0	1.5	23	14	15.6
16	9.9	-2.0	4.0	26	17	17.6

AoA=aortic annulus; LM=left main coronary ostium; PR=aortic prosthesis; 3DTEE=3-dimensional transesophageal echocariography

Figure 7 shows 3DTEE reconstruction of the distance between the upper edge of aortic prosthesis and LM in 2 different cases.

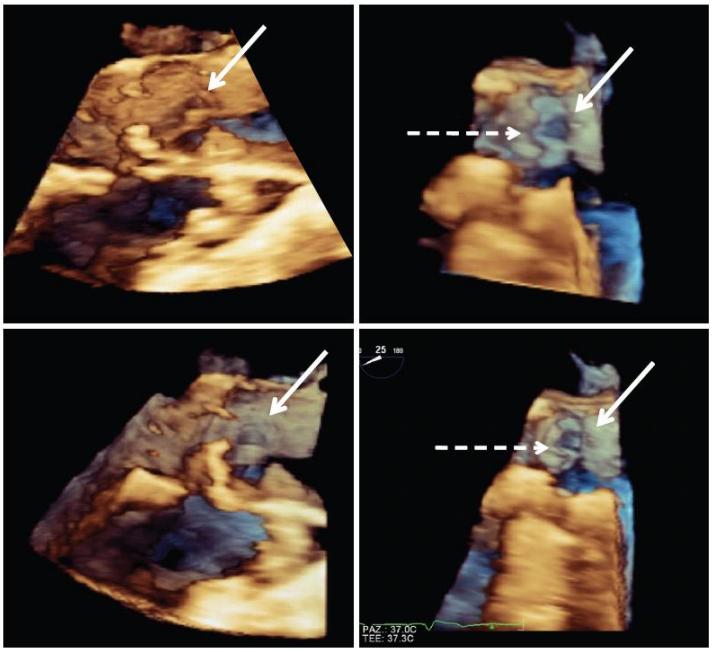

Figure 7. Pre- and post-operative 3DTEE LM visualization. 3DTEE reconstruction of the aortic root and LM in 2 patients before (left panels) and after (right panels) TAVI. Solid arrow indicates the LM coronary ostium; dotted arrow indicates the upper edge of the prosthesis in the postoperative reconstruction. Top panels: pre- and post-operative reconstruction in a patient with the LM coronary ostium in a high position; the upper edge of the prosthesis is a few millimeter distant from the LM. Bottom panels: pre- and post-operative reconstruction in a patient with the LM in a low position; in the post-operative image the upper edge of the prosthesis is partially superimposed on the LM.

There was a good correlation ($r=0.64$, $p<0.001$) between the 3DTEE computed and nominal length of the prosthesis (Figure 8).

No differences in echocardiographic parameters were found in patients with suboptimal hemodynamic results (PPM or AR >2) and cases with optimal hemodynamic results. In particular no correlations were found between prosthesis-mitral leaflet overlap and paravalvular AR or PPM. Moreover no significant correlation was found between LCC length and AoA-LM distance.

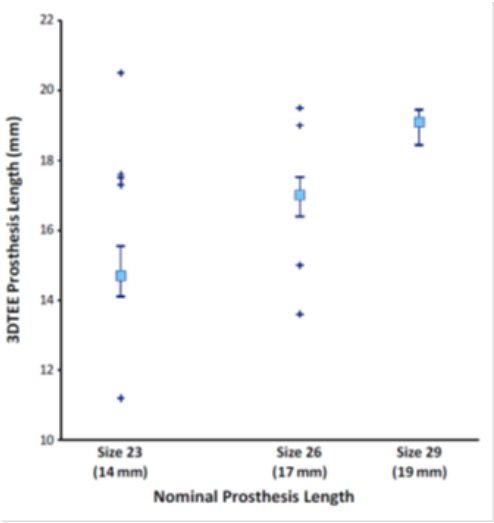

Figure 8. Nominal vs 3DTEE prosthesis length. Correlation between prosthesis nominal length and prosthesis length as measured by 3D transesophageal echocardiography. Median values are depicted as squares; whiskers extend from the first quartile to the third quartile; outliers are shown as + symbols.

Discussion

Transcatheter aortic valve implantation is nowadays a valid alternative to surgical aortic valve replacement for the treatment of surgical high-risk patients with severe aortic valve stenosis. As in traditional surgical aortic valve replacement, after prosthesis implantation an immediate decrease of transvalvular pressure gradient and of systolic left ventricular pressure is expected. These changes are generally associated with a significant increase in coronary flow. [19,20]

However, coronary ostia impairment, due to the presence of low coronary ostia and/or to the occluding effect of the calcified native cusps crushed against the aortic wall after the prosthesis deployment, is included between the possible life-threatening complications of the procedure. [3-5] Moreover, operator-related factors, such as high valve positioning or implantation of an oversized prosthesis, may also lead to postoperative complications.

Several authors [8,10,21] demonstrated the importance of an accurate preoperative evaluation of the distance between AoA and coronary ostia in the selection of subjects candidates for TAVI, in order to avoid LM occlusion due to covering of coronary ostium by the upper part of the prosthesis or by left coronary cusp displacement. Therefore, even in the absence of defined guidelines, an AoA-LM distance lower than 10-11 mm is generally indicated as cut-off value under which a TAVI with Edwards Sapiens prosthesis may be contraindicated. [7,12,18]

Since MDCT provides precise information of the aortic valve anatomy, it is considered the gold standard for the preoperative assessment of TAVI candidates. However, in these critical patients, impaired renal function, severe breathlessness, atrial fibrillation or other arrhythmias are frequently present and may contraindicate the employment of MDCT or limit its image quality.

The position of the coronary arteries relative to AoA can also be assessed using invasive angiography which is often performed in most of the patients preoperatively in order to study coronary arteries and peripheral vessels. However, the angiographic procedure shows the bias due to its 2-dimensional nature and in some cases it may carry an high risk of complications. Therefore MDCT has been reported as a valid alternative to angiography. [9]

The role of echocardiography in the assessment of TAVI patients is well known. The incremental value of 3D echocardiographic technology and its accuracy in comparison to MDCT in the measurement of aortic annulus and ascending aorta dimensions have been also already demonstrated. [8,12,22] Otani et al. [23] evaluated 3DTEE AoA-LM in a large series of patients, however 3D accuracy in comparison with MDCT was calculated only in few cases, all without aortic valve stenosis. Unfortunately in aortic valve stenosis AoA-LM is generally shorter than in controls and the presence of leaflets and AoA calcifications may markedly impair the accuracy of 3DTEE measurements. Moreover, few postoperative data have been reported concerning the distance between left main and aortic prosthesis. [8]

The main findings and novelties of our study are twofold. Firstly, we demonstrated in a large series of aortic patients that a 3DTEE preoperatively estimation of AoA-LM distance is possible in most of them (97%). Only in 3 out of 122 cases LM was not adequately visualized due to poor quality of TEE images. AoA-LM measurement was accurate, comparable to MDCT data and highly reproducible on intra-observer and inter-observer variability. As expected patients with larger AoA dimensions had longer AoA-LM distance and for this reason larger prosthesis could be implanted without coronary impairment.

The second important result is that 3DTEE allows an immediate evaluation of the distance between LM and aortic prosthesis after the implantation. This measurement is feasible in most of the cases (90%) and also accurate. In fact the 3DTEE computed prosthesis length (calculated as the difference between 3DTEE AoA-LM distance plus prosthesis- anterior mitral leaflet overlap, and the distance between LM and the prosthesis) is similar to the prosthetic nominal value. Interestingly in 16 cases the upper edge of the prosthesis exceeded LM ostium, even though none of the enrolled patients had signs or symptoms of ischemia. These data are in accordance with the radiologic (MDCT) observation of Delgado et al. [8]. A possible explanation is the limited extension of the overlap in our

cases (equal or <2 mm) involving a portion of prosthesis where its struts allows coronary inflow, without reaching the reinforced inferior part of the structure where the pericardial leaflets are inserted.

No relation was found between the presence of prosthesis/left main overlap and the prosthesis size or the AoA-LM preoperative distance, supporting the importance of a correct implantation procedure, since even very small changes in the prosthesis positioning may interfere with the coronary flow. This result does not detract much from the necessity of an accurate evaluation of AoA-LM distance. In fact, in high risk patients the knowledge of a small AoA-LM distance is an important information for the operator who may consequently adapt the prosthesis implantation. Indeed our data demonstrate the absence of a significant relation between prosthesis overlap and clinical variables as PPM or paravalvular AR. This observation reinforces the importance of a correct and precise knowledge of AoA-LM distance facilitating optimal and safe procedural maneuvers by the operator.

Moreover after prosthesis deployment in the case of abrupt coronary artery occlusion, the preoperative awareness of a high occlusion risk may favorite the immediate recognition of this life-threatening complication, inducing to a more prompt circulatory support and to the hemodynamic procedure of percutaneous recanalization in order to restore normal coronary flow. In this regard even though the LCC length has been postulated to be involved in this complication, in our patients we did not find prospectively any correlation between this measurement and AoA-LM.

Conclusions

Three dimensional TEE may estimates the AoA-LM distance as an alternative technique to MDCT. Pre and post 3DTEE data concerning the valve and prosthesis morphology and simultaneous real time evaluation of the aortic root including the LM coronary ostium give new insights regarding TAVI and its complications.

Study limitations

Even though we included in the study a high number of cases, only few patients received a 29 mm prosthesis and for this reason the statistical analysis for this group has an important bias as shown in table 2 (no significant correlation was observed between 3DTEE and MDCT for Max-D and area of aortic annulus measurements). However the high correlation in the overall population

between 3DTEE and MDCT measurement confirms the value of 3-dimensional modality and the reported limitation does not detract much from our results.

The right coronary artery was not evaluated in our study and we choose to focus our analysis only to the LM coronary ostium. Few data concerning the measurement by 2D TEE and not 3DTEE have been published regarding the measurement of the distance between right coronary ostium and aortic annulus (12), moreover right ostium is generally more distant from AoA in comparison with LM and its occlusion post-TAVI procedure is very uncommon. Right coronary artery imaging by real-time 3DTEE is more difficult in comparison with the LM one. Even though the incidence of right coronary artery occlusion is low, future studies may define the role of 3DTEE particularly with the new technologies in the evaluation of both coronary ostia before and after TAVI.

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Chapter 4

Intraoperative 2D and 3D transoesophageal echocardiographic predictors of aortic regurgitation after transcatheter aortic valve implantation.

Gripari P, Ewe SH, Fusini L, Muratori M, Ng AC, Cefalù C, Delgado V, Schalij MJ, Bax JJ, Marsan NA, Tamborini G, Pepi M. *Heart 2012*

Abstract

Background. Post-procedural aortic regurgitation (AR) has been described in a large number of patients receiving transcatheter aortic valve implantation (TAVI). Objective The aim of this study was to examine the intraoperative 2-dimensional (2D) and 3-dimensional (3D) echocardiographic features of the aortic valve associated with significant post-procedural paravalvular AR.

Methods. A total of 135 patients (81±7 years) with severe symptomatic aortic stenosis, who underwent TAVI, were imaged with comprehensive 2D and 3D transesophageal echocardiography before the procedure and peri-procedure. Various baseline and peri-procedural echocardiographic characteristics were tested to predict paravalvular AR post-TAVI: calcifications at the aortic valve commissures and leaflets, 'aortic annulus eccentricity index', 'area cover index', overlap between aortic prosthesis and anterior mitral leaflet. Post-procedural paravalvular AR≥2 was considered significant.

Results. Successful TAVI was achieved in all patients. The incidence of paravalvular AR≥2 mmediately after the procedure was 21% (28 patients). Commissural calcifications and, particularly, the calcification of the commissure between the right coronary and noncoronary cusps was significantly more frequent in presence of paravalvular AR; the area cover index pre-TAVI was significantly lower among patients with AR (11.1±11.8% vs 20.8±12.5%, p=0.0004). Multivariate analysis revealed that calcification of the commissure between the right coronary and non-coronary cusps (OR¼2.66, 95% CI 1.39 to 5.12, p=0.001), and the area cover index pre-TAVI (OR=0.95, 95% CI 0.91 to 0.99, p=0.006) were the only independent predictors of significant paravalvular AR after TAVI.

Conclusions. Intraoperative 2D and 3D transesophageal echocardiography identified calcification of the commissure between the right coronary and non-coronary cusps and the area cover index as independent predictors of significant paravalvular AR following TAVI.

Introduction

Over the last few years, transcatheter aortic valve implantation (TAVI) has been demonstrated to be a feasible and effective therapeutic alternative to traditional aortic valve replacement for high-risk surgical patients with symptomatic severe aortic stenosis. [1-7] Single- and multi-center studies showed significant improvements after TAVI in symptoms and quality of life together with excellent transvalvular haemodynamic characteristics and good survival rates at 2 years follow up. [5, 8, 9]

However, post-procedural aortic regurgitation (AR), mainly paravalvular, has been described in a relatively large number of patients after TAVI. [1-3, 5, 7-10] The majority of patients with paravalvular AR after TAVI shows mild grade regurgitation and the incidence of moderate or severe paravalvular AR is low (7% at 1 year and 6,9% at 2 years in the PARTNER trial).[6] However, understanding the mechanisms and potential determinants of paravalvular AR after TAVI is of importance to minimize the incidence of this complication and therefore its potential impact on left ventricular (LV) performance and clinical outcome.

Initial studies have proposed multi-detector computed tomography as a valuable imaging tool to achieve an accurate characterization of the aortic valve apparatus and to ensure high procedural success rate.[11] However, in clinical practice, transesophageal echocardiography (TEE) is commonly the first imaging technique of choice to accurately characterize valvular morphology and geometry, both before and during the procedure, and to evaluate the results after TAVI. Therefore, the aim of this study was to identify potential predictors of significant paravalvular AR occurring immediately after TAVI, using intraoperative 2D and 3D TEE.

Methods

A total of 135 consecutive patients, who underwent TAVI with the Edwards-Sapien valve between November 2007 and January 2010 in 2 centers (Centro Cardiologico Monzino, IRCCS, Milan, Italy and Leiden University Medical Center, Leiden, The Netherlands), were included. TAVI was performed using the transfemoral or transapical approach, according to the peripheral artery anatomy. A 23-mm device was implanted when, as measured on 2D TEE images, the diameter of the aortic annulus (AoA) was > 18 mm and ≤ 21 mm, and a 26-mm device was implanted when the diameter of the AoA was > 21 mm and ≤ 25 mm.

Two-dimensional transthoracic echocardiography was performed before the procedure and before discharge to assess LV volumes and ejection fraction (EF), as well as to measure transaortic pressure gradients and aortic valve area normalized for body surface area (AVAi) according to current recommendations. [12] Aortic stenosis was defined as severe in the presence of a mean transaortic pressure gradient (MPG) greater than 40 mmHg or an AVAi < 0,6 cm^2/m^2 . [13, 14]

All patients were imaged with comprehensive peri-procedural 2D and 3D TEE, in the operating room. TEE was performed using the iE33 ultrasound system (Philips Medical Systems, MA) equipped with fully-sampled matrix-array 3D probe (model X7-2t) and various baseline and procedural variables were evaluated to predict significant paravalvular AR. All the measurements, based on 2D and 3D TEE, were performed intraoperatively. Pre-procedural measurements were obtained before prosthesis deployment, blind to the outcome of the procedure.

2D transesophageal echocardiography

Two-dimensional measurements of the AoA were performed, as recommended [15], during early systole in the long-axis view at approximately the 120° angle, at the hinge points of the leaflets. The presence and the distribution of aortic valve calcifications was evaluated in the short-axis view of the valve at approximately the 30°-60° angle. The amount of aortic calcifications was assessed, separately for the commissural and for the central regions of the cusps, using a semiquantitative score (0-4), as depicted in Figure 1: 0= no calcifications; 1= (minimal), speckles; 2= (mild) single nodule; 3= (moderate) two or more nodules; 4= (severe) diffuse, confluent calcifications. [16] A score was assigned to each cusp and commissure. An overall grade, ranging from 0 to 12, resulted from the sum of the three cusps and from the sum of the three commissures, respectively. Furthermore, whether the distribution of the calcifications was symmetric or not was noted.

Aortic valve regurgitation, if present before the procedure, was recorded and quantified according to standard echocardiographic color-Doppler method (semiquantitative score: 0-4). [17]

After TAVI, aortic prosthesis overlap with the anterior mitral leaflet was measured at the 2D long-axis view as the length between the junction point of the prosthesis with the right sinus of Valsalva and the ventricular free edge of the prosthesis.

The presence of post-procedural paravalvular AR was evaluated immediately after the device deployment and after removal of the catheter and the guidewire. Post-procedural paravalvular AR was quantified according to standard echocardiographic color-Doppler method using the jet width and extension and graded as: 0 (absent), 1 (mild), 2 (mild to moderate), 3 (moderate to severe), 4 (severe). In the presence of multiple paravalvular AR jets, visualized in the short- and long-axis TEE

views, paraprosthetic, AR was expressed as an overall grade. Paravalvular AR was considered significant if ≥ 2.

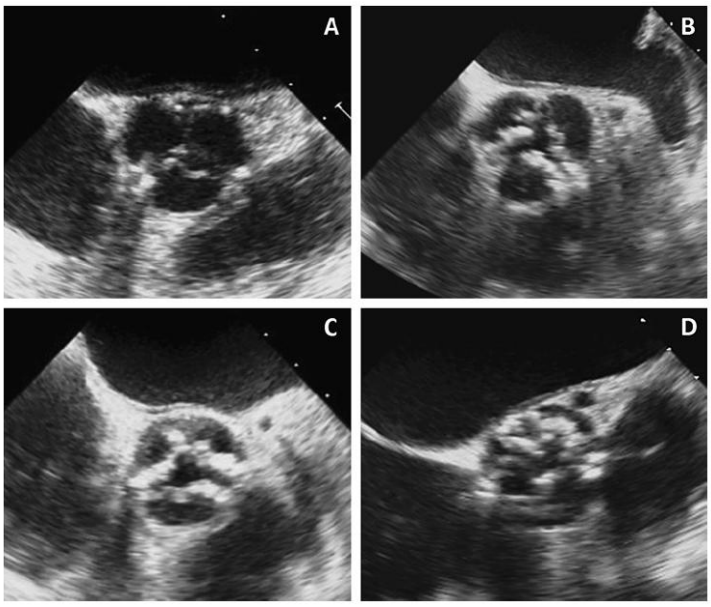

Figure 1. Examples of different degrees of aortic valve calcification assessed using a semiquantitative score: 1= minimal (panel A), 2= mild (panel B), 3= moderate (panel C), 4= severe calcifications (panel D).

3D transesophageal echocardiography

Measurements on 3D datasets were obtained using the QLAB 3DQ software (Philips Medical System, Andover, MA, USA) available on the echocardiographic system. Three-dimensional measurements of the AoA were performed during early systole in a true cross sectional plane. In detail, 3D live and full volume images were acquired in order to obtain the visualization of a magnified aortic root in the 30° short-axis or the 120° long-axis view. The 3D datasets were cropped using two orthogonal planes through the long-axis of the LV outflow tract. A third transverse plane was positioned parallel and immediately below the aortic valve. This ensured a true “en face” view of the AoA, from which the shortest and the longest annulus diameters were measured. Annulus eccentricity was defined as 1 - the ratio between the shortest and the longest annulus diameter, so that a perfect circle has an eccentricity index of zero, while a higher eccentricity index represents a more elliptical geometry. Moreover in the same “en face” view, the annulus area was measured by planimetry. The "area cover index" was defined as the percentage difference between planimetered AoA area and the nominal prosthesis area (1 - annulus area/ prosthesis nominal area). The nominal prosthesis area was calculated on the basis of the pre-specified diameter of the available prosthesis (23 or 26 mm) supplied by the manufacturer (415 mm^2 for a prosthetic diameter of 23 mm, 531 mm^2

for the 26 mm diameter prosthesis). This index indicates a correspondence between the two areas when it is close to 0. When the planimetered aortic annular area is smaller compared to the nominal prosthesis area the cover index is higher. Figure 2 shows an example of the measurements of the native planimetered AoA in an 3D true cross-sectional plane.

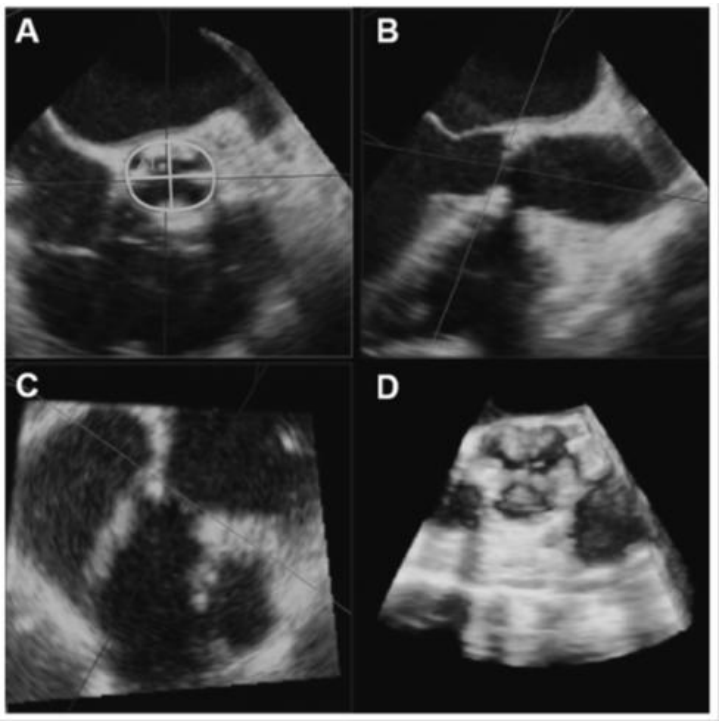

Figure 2. Measurements of the native planimetered aortic annulus in a 3D true cross sectional rendering pre-TAVI. Orthogonal diameters and planimetered area of the annulus (Panel A) are obtained through correct alignment based on 3D dataset.

Moreover, immediately after the procedure in a 3D true cross-sectional plane of the aortic prosthesis at the level of the cusps, the device eccentricity index was calculated using the shortest and the longest diameter and the planimetered prosthesis area was traced adopting the internal dimensions of the prosthetic valve (Figure 3). In addition, the actual planimetered prosthesis area was compared both with the annulus planimetered area pre-TAVI (1-Planimetered Prosthesis/Planimetered Annulus) and with the prosthesis expected area calculated on the basis of the pre-specified diameter of the available prosthesis (1- Planimetered Prosthesis/ Prosthesis Nominal Area); the percentage difference was then recorded.

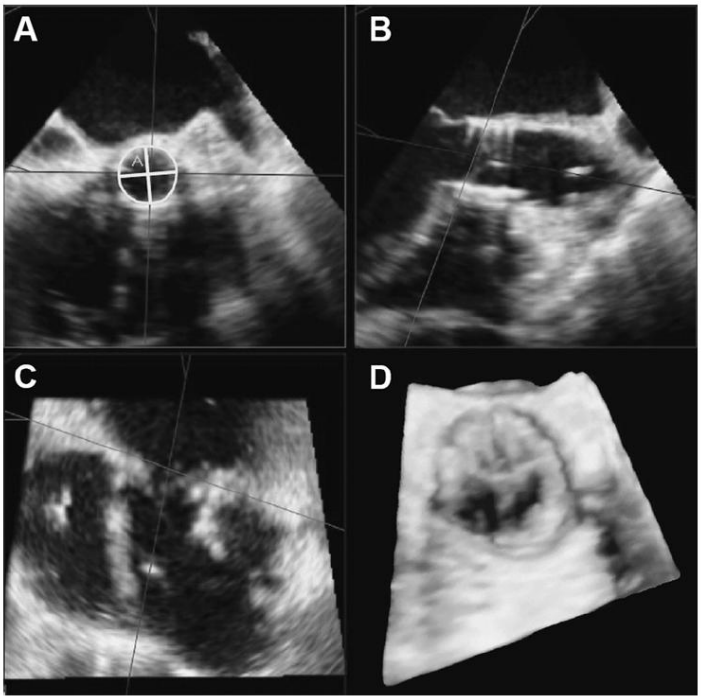

Figure 3. 3D aortic annulus after TAVI. Annulus measurements were performed after TAVI adopting the internal dimensions of the prosthetic valve and methods as in Figure 1.

Statistical Analysis

Continuous data are presented as mean±SD and categorical variables as frequency or percentages, as appropriate. A normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Differences between patients with paravalvular AR<2 and patients with paravalvular AR≥2 were assessed with unpaired Student's t test or Mann-Whitney U test for continuous variables, as appropriate, and with Chi-square test or Fisher's exact test for categorical variables. Several clinical and echocardiographic characteristics pre-TAVI were tested in a univariate logistic regression analysis in order to evaluate whether some characteristics before the procedure could help predicting the development of significant AR after TAVI. Significant variables in univariate analysis were included in a multivariate logistic regression analysis with stepwise method for the identification of independent variables predicting paravalvular AR≥2. Goodness-of-fit was assessed using the Hosmer and Lemeshow test, in which a p value <0.05 indicated a lack of fit of the model. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL).

Measurements were performed by two different operators, one per each involved Institution. The inter-observer variability has been assessed in terms of coefficient of variation (the ratio of

standard deviation of the differences to the mean value) and 95% limits of agreement at Bland-Altman analysis between repeated measurements on a randomly chosen subset of 25 patients.

Results

Successful TAVI, defined as correct positioning and successful device deployment within the aortic valve without periprocedural major adverse cardiovascular and cerebral events, was reached in all patients. Paravalvular AR immediately post-TAVI was graded: 0 in 42 patients, 1 in 65 patients, 2 in 25 patients, 3 in 2 patients and 4 in 1 patient. The incidence of paraprosthetic AR≥2 was 21% (28 patients) immediately after the procedure. Of note, of the three patients with AR≥3 immediately after the procedure, one patient (AR=4) underwent the implantation of a second device, while in the remaining two patients balloon inflation was repeated and the maximal expansion of the valve was reached, with a significant decrease of paraprosthetic AR.

AoA parameters were found to be highly reproducible on inter-observer variability (coefficient of variation: shorted diameter 4.9%, longest diameter 4.1%, planimetered area 8.8%). Moreover, the results of Bland-Altman analysis showed limited bias and narrow limits of agreement (shorted diameter: bias 0.9 mm – LOA: 2.7 mm, longest diameter bias 0.0 mm – LOA: 3.3 mm, AoA planimetered area bias 0.3 cm^2 – LOA: 1.0 cm^2)

Baseline clinical and echocardiographic characteristics

Main clinical and echocardiographic characteristics of the overall patient population and for each group (according to the presence of post-TAVI paravalvular AR<2 and AR≥2) are listed in Table 1. Clinical parameters did not show significant differences among the 2 groups. All patients had severe aortic stenosis (AVAi 0.38±0.10 cm^2/m^2, MPG 47±16 mmHg). The AR grade before TAVI was similar between the study groups. In addition, LV volumes and EF were not significantly different between the groups. The mean annulus eccentricity index pre-TAVI was 0.11±0.08 and the mean “area cover index” was 18.5±13.0%. A trend towards a higher annulus eccentricity index was observed among patients with significant paravalvular AR and the “area cover index” was significantly lower among patients with significant paravalvular AR.

The total amount of commissural calcifications, measured semi-quantitatively, was respectively: 0-4 in 13%, 5-8 in 74%, 9-12 in 13% of the patients. The total amount of commissural calcifications was significantly higher among patients with significant paravalvular AR ≥ 2 (Table 1). The commissure between the right coronary and non-coronary cusps was the most heavily calcified in

24% of cases and was more frequently calcified among subjects with AR ≥ 2 ($p<0.05$). The amount of central calcifications was 0-4 in 16% of the patients, 5-8 in 62% of the cases and 9-12 in 22% of the aortic valves. In 24% of the aortic valves the non-coronary cusp was the most calcified, followed by the right coronary (14%) and left coronary cusp (9%). Twenty-two percent showed a symmetric distribution of valve calcifications in all the three cusps (Table 1).

Table 1. Baseline clinical and echocardiographic characteristics together with pre-procedural amount and distribution of aortic valve calcifications of the whole population, and separately for patients without and with significant paravalvular aortic regurgitation (AR).

Variables	Overall (n=135)	AR < 2 (n=107)	AR ≥ 2 (n=28)	p-value
Age (years)	81±7	81±7	81±8	0.982
Sex (male)	61 (45%)	44 (41%)	17 (61%)	0.064
Body surface area (m^2)	1.8±0.2	1.8±0.2	1.8±0.2	0.899
Logistic EuroSCORE (%)	22.3±12.9	23.7±14.3	18.0±5.1	0.136
STS score	9.9±8.7	10.3±9.2	8.1±6.2	0.427
Angina	19 (29%)	16 (31%)	3 (21%)	0.741
Dyspnoea	60 (91%)	47 (90%)	13 (93%)	1.000
Syncope	20 (30%)	16 (31%)	4 (29%)	1.000
CAD	36 (54%)	29 (56%)	7 (50%)	0.768
Previous CABG	9 (14%)	9 (17%)	0 (0%)	0.186
Previous PCI	16 (24%)	14 (27%)	2 (14%)	0.488
Previous MI	12 (18%)	11 (21%)	1 (7%)	0.436
HBP	59 (89%)	46 (88%)	13 (93%)	1.000
Hcholest	34 (52%)	27 (52%)	7 (50%)	1.000
Diabetes Mellitus	17 (26%)	13 (25%)	4 (29%)	0.744
PVD	26 (39%)	20 (38%)	6 (39%)	0.768
Smoking	23 (35%)	18 (35%)	5 (36%)	1.000
Atrial Fibrillation	8 (12%)	7 (13%)	1 (7%)	1.000
Paced at baseline	5 (8%)	4 (8%)	1 (7%)	1.000
LV EDVi PRE (mL/m^2)	61±22	60±21	64±24	0.378
LV ESVi PRE (mL/m^2)	29±18	28±18	33±20	0.273
EF PRE (%)	55±12	55±13	52±12	0.136
AVAi PRE (cm^2/m^2)	0.38±0.10	0.38±0.10	0.37±0.08	0.678
AO MPG PRE (mmHg)	47±16	47±16	48±18	0.786
AO regurgitation PRE (0-4)	1.01±0.79	0.99±0.84	1.11±0.57	0.490
Annulus TEE (mm)	22±2	22±2	22±2	0.393
Annulus eccentricity index PRE	0.11±0.08	0.11±0.08	0.12±0.07	0.067
Area cover index PRE (%)	18.5±13.0	20.8±12.5	11.1±11.8	0.0004

Continue

Variables	Overall (n=135)	AR < 2 (n=107)	AR ≥ 2 (n=28)	p-value
Commissural calcifications				0.013
0-4	18 (13%)	16 (15%)	2 (7%)	
5-8	100 (74%)	82 (77%)	18 (64%)	
9-12	17 (13%)	9 (8%)	8 (29%)	
Central calcifications				0.121
0-4	22 (16%)	20 (19%)	1 (4%)	
5-8	84 (62%)	66 (62%)	19 (68%)	
9-12	29 (22%)	21 (19%)	8 (28%)	
Most Calcified Commissure %				
Symmetric calcification without commissure accentuation	72 (53%)	55 (51%)	17 (61%)	0.38
Non coronary - Left coronary cusp	16 (12%)	16 (15%)	0 (0%)	0.28
Non coronary - Right coronary cusp	32 (24%)	21 (20%)	11 (39%)	<0.001
Left coronary - Right coronary cusp	15 (11%)	15 (14%)	0 (0%)	0.17
Most Calcified Cusp %				
Symmetric calcification without cusp accentuation	72 (53%)	59 (55%)	13 (46%)	0.41
Non coronary cusp	32 (24%)	25 (24%)	7 (25%)	0.26
Left coronary cusp	12 (9%)	9 (8%)	3 (11%)	0.67
Right coronary cusp	19 (14%)	14 (13%)	5 (18%)	0.15

Data are expressed as mean 6 SD for continuous variables or as number (percentage) for categorical data; p value for comparison between AR <2 and AR ≥2. AO, aortic; AVAi, indexed aortic valve area; CAD, coronary artery disease; CABG, coronary artery bypass grafting; EF, ejection fraction; HBP, high blood pressure; Hcholest, hypercholesterolaemia; LV EDVi, indexed left ventricular end-diastolic volume; LV ESVi, indexed left ventricular end-systolic volume; MI, myocardial infarction; MPG, mean pressure gradient; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; TEE, transesophageal echocardiography.

Echocardiographic characteristics after TAVI

TAVI was performed through the transfemoral approach in 69 patients (51%) and through the transapical access in 66 patients (49%). Out of 135 patients, 47 patients (35%) received a 23-mm valve, while 88 patients (65%) received a 26-mm valve; there was no difference regarding valve size between the two groups with and without significant paravalvular AR. As shown in Table 2, all patients showed improvements in transvalvular hemodynamics (AVAi 1.14±0.26 cm^2/m^2, MPG 11±4 mmHg).

After TAVI, AoA eccentricity index decreased (0.06±0.05) (Table 2). The mean prosthesis planimetered area post-TAVI was 323±52 mm^2 in patients with a 23-mm device and 385±50 mm^2 in patients with a 26-mm device. The prosthesis planimetered area post-TAVI was 7.3±17.4% smaller than the native annulus area pre-TAVI; this percentage difference was similar among subjects with

and without AR. The difference between the planimetered prosthesis area and the nominal prosthesis area was significantly lower in presence of paravalvular AR≥2, suggesting a certain degree of undersizing of the prosthesis despite proper expansion of the device. In addition, the length of aortic prosthesis overlap with anterior mitral leaflet was 5±2 mm, without any significant difference between the two groups.

Table 2. Echocardiographic characteristics after TAVI.

Variables	Overall (n=135)	AR < 2 (n=107)	AR ≥ 2 (n=28)	p-value
LV EDVi POST (mL/m^2)	58±26	56±26	61±22	0.126
LV ESVi POST (mL/m^2)	27±19	26±19	35±18	0.602
EF POST (%)	56±11	57±11	51±11	0.073
AVAi POST (cm^2/m^2)	1.14±0.26	1.15±0.27	1.11±0.21	0.319
AO MPG POST (mmHg)	11±4	11±5	10±4	0.734
Annulus eccentricity index POST	0.06±0.05	0.06±0.05	0.05±0.04	0.686
1-Planimetered Prosthesis/Planimetered Annulus	7.3±17.4	7.6±15.1	6.4±23.3	0.637
1-Planimetered Prosthesis/Prosthesis Nominal Area	25.8±10.7	27.9±8.5	18.6±4.0	0.002
Prosthesis overlapping (mm) with MV	5±2	5±2	5±1	0.766

Data are expressed as mean 6 SD or median (258 percentilee758 percentile) for continuous variables; p value for comparison between AR <2 and AR ≥2. AO, aortic; AR, aortic regurgitation; AVAi, indexed aortic valve area; MPG, mean pressure gradient; MV, mitral valve.

Determinants of paravalvular AR

At the logistic regression analysis, the pre-TAVI univariate determinants of paravalvular AR≥2 post-TAVI were the degree of the commissural calcifications of the native valve, the calcification of the commissure between the right and the non-coronary cusps and the “area cover index” pre-TAVI. Multivariate analysis revealed that calcification of the commissure between the right coronary and non-coronary cusp (OR=2.66, 95%CI, p=0.001) and the area cover index pre-TAVI (OR=0.95, 95% CI, p=0.006) were the only independent predictors of the presence of significant paravalvular AR (R^2=0.52). The model displayed satisfactory goodness-of-fit (p=0.26).

Discussion

The main findings of the current study are the following: a) 3D-TEE allows a complete and detailed evaluation of the anatomy of the aortic valve apparatus before the procedure, as well as of

the prosthetic valve immediately after TAVI, b) the degree of calcification, particularly of the commissure between the right coronary and non-coronary cusps, and "area cover index" represent independent predictors of significant paravalvular AR.

Many trials have shown that TAVI is feasible and provides haemodynamic and clinical improvement in high-risk patients with symptomatic severe aortic stenosis. [3,5,8-10] However, the development of post-procedural paravalvular AR is one of the most frequent complications after TAVI. Although previous studies showed that paravalvular AR was mild in the majority of cases [1,5], the long-term consequences of paravalvular leaks are not well-established. [18-21] Significant paravalvular AR post-TAVI may be due to several factors, including device malpositioning, erroneous device sizing and presence of severely calcified native valves. [11, 22, 23] Therefore, the analysis of the mechanisms and the identification of potential determinants of significant paravalvular AR post-TAVI is important to prevent the occurrence of this complication.

Aortic valve calcifications

Incomplete device expansion due to aortic valve calcifications is believed to be one of the contributing factors to paravalvular AR post-TAVI. [23] In fact, heavily calcified native aortic valves may not allow a perfect apposition of the device along the annulus circumference. This has been demonstrated in experimental series and in clinical series by using multi-detector computed tomography. [24-26] Delgado et al.[11] found that patients with moderate aortic regurgitation post-TAVI showed more calcified native valves, as quantified by Agatston calcium score, in particular at the level of the commissures. Koos et al.[24] emphasized that patients with severe aortic valve calcification had an increased risk of significant paravalvular AR as well as a trend of an increased need for second transcatheter maneuvers (re-ballooning) after TAVI. Moreover, Zegdi et al.[26], trying to define the precise characteristics of a self-expandable aortic stent deployment in humans, found that stent misdeployment, with a triangular or elliptical shape, occurred in one-third of cases of tricuspid valves; in these patients a gap between the external surface of the stent and the inner surface of the native aortic valve was identified and located exclusively at the level of the commissures; this may occur when part of the stent frame lies on top of a large calcification. Our results, based on intra-operative 3D TEE, confirm these previous findings, showing that the calcifications of the commissure between the right coronary and non-coronary cusp is related to significant post-procedural paravalvular AR.

Area cover index

Current recommendations include echocardiography as a valuable method to size the AoA diameter and to select the correct prosthesis size.[8] Although caution was recommended regarding

the underestimation of the annular cross-sectional area, due to its elliptical geometry, no suggestions were provided to overcome this problem. 3D TEE, as previously reported by Ng et al. [27], allows a direct tracing the planimetered area of the AoA without geometric assumptions: despite a 3D underestimation of annulus area compared to the same measurement performed with computed tomography, considered as the gold standard, a good correlation with narrow limits of agreement was found between the two methods.

Considering the fact that the 3D echocardiographic measurement of the AoA is feasible and accurate, we tried to identify a relationship between the planimetered annular area, the nominal prosthesis expected area and the presence of post-TAVI paravalvular AR. The area cover index pre-TAVI was significantly lower among patients with significant post-procedural paravalvular AR, suggesting that a certain degree of prosthesis oversizing is needed to ensure a good procedural result. Similarly, Detaint et al. [28] found a significant relationship between large annulus size and the occurrence of significant paravalvular AR; to appraise the congruence between annulus and device they used a "cover index" that compared 2D echocardiographic AoA diameter and prosthesis diameter and found a significant relationship between low cover index and AR.

In addition, the multivariate logistic regression analysis performed in this study demonstrated that, calcification of the commissure between the right coronary and non-coronary cusp and a low "area cover index" pre-TAVI were also independent and reliable predictor of post-procedural significant paravalvular AR. Therefore, important morphological aspects, related to the severity as well as the localization of valvular calcification, may play a role in the development of paravalvular aortic regurgitation, leading to an abnormal deployment of the prosthesis in terms of irregular shape or inadequate adhesion of the prosthesis itself to the native valve. Moreover, a low "area cover index" predicts the development of significant post-procedural paravalvular AR suggesting that this index could be utilized as an additional parameter when choosing the prosthetic size in all those patients with borderline 2D TEE annulus size. The "area cover index" and the availability of larger prostheses may reduce the incidence of significant paravalvular AR, avoiding prosthetic undersizing and simultaneously allowing a better fit.

Evaluation of prosthesis deployment with 3D TEE

To date, few studies have evaluated the deployment characteristics of the transcatheter bioprosthesis. [11,27,28] In this field 3D TEE may provide a good visualization of the device, allowing the assessment of the quality of its expansion and its positioning with respect to near structures. Our data demonstrated that a 3D TEE morphological evaluation of the device post TAVI was feasible in

135 patients in a routine clinical setting, allowing the assessment of several parameters. Among our 135 patients the mean prosthesis planimetered area post-TAVI was 323±52 mm^2 and 385±50 mm^2 in patients with a 23 mm and 26 mm device, respectively. The prosthesis planimetered area post-TAVI was approximately 7.3±17.4% smaller than the native annulus area pre-TAVI in the whole population (and with no differences between patients with and without significant paravalvular AR), suggesting a satisfactory prosthesis deployment. Despite the successful deployment, the prosthesis planimetered area remained smaller than the annulus area pre TAVI mainly because the actual dimension of the device expansion is limited by the annular stiffness and the severity of cusps and commissural calcifications. Moreover, the implanted prosthesis does not reach "in vivo" the expected nominal area as previouslty described.[29] In the current study, the difference between planimetered and nominal prosthesis area was significantly lower in patients with paravalvular AR ≥ 2 compared to patients without regurgitation, suggesting a proper deployment of a relatively undersized device.

Study limitations

This study considers only the balloon-expandable valve. However, the aim of this study was not to compare the echocardiographic predictors of aortic regurgitation in different devices. In addition, the precise quantification of aortic regurgitation following TAVI is still problematic and relies only on color-Doppler imaging; further studies are needed to clarify this topic. Furthermore, only a limited number of variables pre-procedure were tested in the regression analysis, given the relatively few cases with significant AR. In the present series, patients with paravalvular AR have asymmetrically calcified valves with a high frequency of calcification of the commissure between the right coronary and non-coronary cusp. However, the relatively limited number of patients with significant paravalvalvular AR preclude us to observe significant differences in terms of other location of calcifications.

Finally, a limitation of this study could be the absence of a comparison between 3D TEE AoA measurements and respective values obtained in the same subjects from other 3D radiologic technique, such as computed tomography. However, the assessment of the accuracy of 3D TEE imaging versus other techniques was beyond the scopes of this study, which was based on the most widely available imaging approach, also feasible in the operatory theatre.

Conclusions

This study suggests that intraoperative 2D and 3D TEE may allow the identification of predictors of significant paravalvular AR following successful TAVI. In particular, the presence of heavily calcified commissure between the right coronary and non-coronary cusp and the measurement of “area cover index” should be considered during patient selection for TAVI in order to minimize the development of significant paravalvular AR after the procedure.

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Chapter 5

Aortic annulus area assessment by multidetector computed tomography for predicting paravalvular regurgitation in patients undergoing balloon-expandable transcatheter aortic valve implantation: a comparison with transthoracic and transesophageal echocardiography.

Pontone G, Andreini D, Bartorelli AL, Bertella E, Cortinovis S, Mushtaq S, Annoni A, Formenti A, Baggiano A, Conte E, Tamborini G, Muratori M, **Gripari P**, Bovis F, Veglia F, Foti C, Alamanni F, Ballerini G, Fiorentini C, Pepi M. *Am Heart J. 2012*

Abstract

Background. Transcatheter aortic valve implantation (TAVI) is a valid alternative to surgery in high-risk patients with severe aortic stenosis. Aortic annulus (AoA) sizing is crucial for TAVI success. The aim of the study was to compare AoA dimensions measured by multidetector computed tomography (MDCT) vs those obtained with transthoracic (TTE) and transesophageal echocardiography (TEE) for predicting paravalvular aortic regurgitation (PAR) after TAVI.

Methods. Aortic annulus maximum diameter, minimum diameter, and area were assessed using MDCT and compared with TTE and TEE diameter and area for predicting PAR after TAVI in 151 patients (45 men, age 81.2±6.4 years).

Results. Aortic annulus maximum, minimum diameter, and area detected by MDCT were 25.04±2.39 mm, 21.27±2.10 mm, and 420.87±76.10 mm2, respectively. Aortic annulus diameter and area measured by TTE and TEE were 21.14±1.94 mm and 353.82±64.57 mm2 and 22.04±1.94 mm and 384.33±67.30 mm2, respectively. A good correlation was found between AoA diameters and area evaluated by MDCT vs TTE and TEE (0.61, 0.65, and 0.69 and 0.61, 0.65, and 0.70, respectively), with a mean difference of 3.90±1.98 mm, 0.13±1.67 mm, and 67.05±55.87 mm2 and 3.0±2.0 mm, 0.77±1.70 mm, and 36.54±56.43 mm2, respectively. Grade $\geq$2 PAR occurred in 46 patients and was related to male gender, higher body mass index, preprocedural aortic regurgitation, and lower mismatch between the nominal area of the implanted prosthesis and AoA area detected by MDCT.

Conclusions. Mismatch between prosthesis area and AoA area detected by MDCT is a better predictor of PAR as compared with echocardiography mismatch. Specific MDCT-based sizing recommendations should be developed.

Introduction

After many years of research and development, transcatheter aortic valve implantation (TAVI) has become a reproducible and effective alternative to conventional aortic valve replacement for patients with severe and symptomatic aortic stenosis (AS) who are considered to be at high surgical risk. Despite being less invasive, TAVI may be associated with serious complications. Among them, moderate to severe para-valvular regurgitation (PAR) occurs in 7% to 20% of patients [1-4] and is associated with increased in-hospital and late mortality. The negative impact of moderate to severe PAR on clinical outcome is a compelling motivation to perform studies for assessing anatomic and procedural-related predictors of this complication in order to guide patient evaluation before and during TAVI. Transthoracic (TTE) and transesophageal echocardiography (TEE) have been used for aortic annulus (AoA) measurement in order to choose a prosthesis of appropriate size. [5, 6] However, prosthesis sizing with both imaging techniques is based on the assumption that AoA has a circular shape. On the contrary, recent studies with multidetector computed tomography (MDCT) demonstrated that AoA is frequently elliptical. [7-10] Moreover, TTE and TEE may underestimate AoA size as compared to MDCT.[8, 11] Therefore, we sought to compare the measurement of AoA area by MDCT using planes transecting the axis of the aortic root versus AoA evaluation by TTE and TEE based on the geometrical assumption that AoA is circular and to assess their relationship with PAR after TAVI in patients treated with the Sapien prosthesis.

Methods

Between April 2008 and April 2011, 260 consecutive patients with severe AS were referred to our institute for TAVI. In 11 patients (7%), TAVI was not performed because of contraindications, while 3 (2%) patients were treated with surgical valve replacement due to complications occurring during the percutaneous procedure.

Exclusion criteria for MDCT prior to TAVI were severe impaired renal function (creatinine clearance <30 ml/min), inability to sustain a 10-s breath hold, atrial fibrillation or other cardiac arrhythmias, and heart rate (HR) ≥70 bpm despite an oral dose of ivabradine (10 mg/die for 24-48 hours before MDCT) administered in patients with a resting HR ≥70 bpm. According to the exclusion criteria, 47 (18%) patients did not undergo MDCT, while MDCT evaluation was performed without ECG gating in 48 patients (18%), respectively. Thus, a total of 151 patients were included in the study

(45 men, mean age 81.2±6.4 years). Written informed consent was obtained from all patients and the study protocol was approved by the local ethical committee.

Echocardiography protocol

In all patients, TTE was obtained using a commercially available system (IE33 system, Philips Medical System, MA) at baseline and after TAVI. For each patient, end-diastolic (EDV), end-systolic (ESV) left ventricle volumes and ejection fraction (EF) were measured.. The severity of AS was assessed by the peak and mean aortic gradients, while the aortic valve area was calculated with the continuity equation. AS was graded according to the American College of Cardiology/American Heart Association guidelines.[12]

Aortic regurgitation was graded as none (grade 0), mild (grade 1), mild to moderate (grade 2), moderate (grade 3) or severe (grade 4) according to published guidelines. [12]

Measurement of AoA-diameter (AoA-D) by TTE and TEE were performed in systole in a parasternal long-axis view on the left ventricular outflow tract at the point of insertion of the right and non-coronary aortic leaflets (Figure 1A and 1B). The AoA-area was estimated using the following equation $(AoA\text{-}D_{TTE}/2)^2*\Pi$ with the assumption that they are circular. PAR was assessed immediately following valve implantation and thereafter at 30 days. It was classified into 4 grades as previously described. [12] PAR ≥2/4 was defined as significant.

To evaluate whether a wrong positioning of the prosthesis could be the cause of PAR, the final position of the valve was assessed reviewing TEE and fluoroscopy images in all patients with PAR≥2. A wrong position was identified when the inflow of prosthesis was above the basal insertion of the native leaflets or when the outflow portion of the sealing cuff was above the basal insertion of the native leaflets.

Patient-prosthesis mismatch was defined as the difference between the prosthesis area and both AoA-area measured by TTE and TEE. To appraise the congruence between the AoA and device a "cover index" expressed as a ratio of: 100x[(prosthesis area – TTE and TEE area)]/prosthesis area was measured as well.

MDCT protocol

The MDCT exams were performed with a LightSpeed VCT XT or Discovery HD750 scanner (GE Healthcare, Milwaukee, WI) with the slice configuration 64 x 0.625 mm. All patients received a triple-injection protocol of an 80-ml bolus of contrast (Iomeron 400 mg/ml, Bracco, Milan, Italy) through an antecubital vein at an infusion rate of 5 ml/s, followed by 50 ml of saline solution and an additional 50-ml contrast bolus at 3.5 ml/s using fluoroscopic trigger method.

AoA was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets. [13] For each AoA, maximum diameter, minimum diameter and area were measured in systole in an orthogonal plane on the center line of the aorta. (Figure 1 Panel C to E).

Finally, patient-prosthesis mismatch was defined as the difference between the nominal area of the prosthesis implanted and the AoA-area derived by maximum and minimum diameters using the following equation $(AoA\text{-}D_{TTE}/2)^2*\Pi$ with the assumption that they are circular or versus the AoA-area directly measured by MDCT. The congruence between the AoA and device a "cover index" expressed as a ratio of: 100x[(prosthesis area – MDTC area)]/prosthesis area was estimated as well.

Each MDCT variable was measured twice by one of the investigators (GP), while another blinded reader (GB) measured the same MDCT variables once again to test the intra-observer and inter-observer variability.

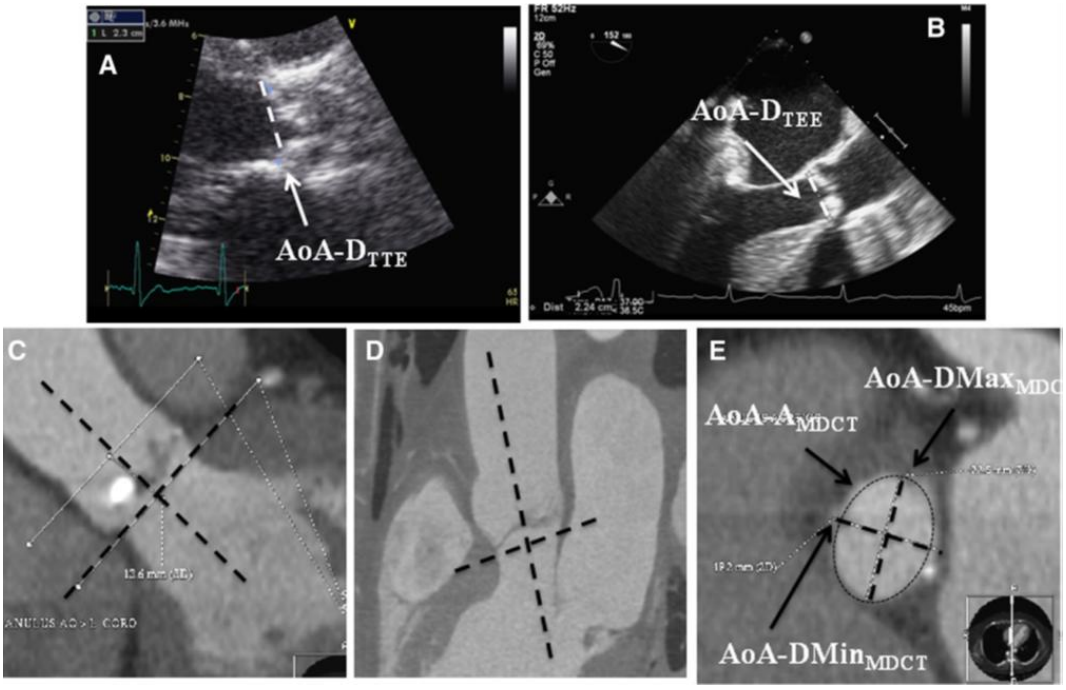

Figure 1. Methodology for the assessment of the AoA. A, TTE: the AoA-D was measured in mid-systole by TTE ($AoA\text{-}D_{TTE}$) in a parasternal long-axis view on the left ventricular outflow tract at the point of insertion of the right and non-coronary aortic leaflets. B, TEE: the AoA-D was measured in mid-systole by TEE ($AoA\text{-}D_{TEE}$) in the mid-esophageal long-axis view (120° to 140°) on the left ventricular outflow tract at the point of insertion of the right and non-coronary aortic leaflets. C-E, MDCT: the AoA evaluated by MDCT (AoA_{MDCT}) was defined as a virtual ring formed by joining the basal attachments of the aortic leaflets. AoA_{MDCT} maximum diameter ($AoA\text{-}DMax_{MDCT}$), minimum diameter ($AoA\text{-}DMin_{MDCT}$) and area ($AoA\text{-}A_{MDCT}$) were measured in an orthogonal plane on the center-line of the aorta obtained in oblique coronal and oblique sagital views, respectively.

TAVI procedure

All procedures were performed by a combined team of cardiologists, cardiac surgeons and anesthesiologists working together in a dedicated hybrid room in general anesthesia. The Sapien valve (Edwards Lifesciences Inc, Irvine, CA) in three different sizes (23-mm, 26-mm and 29-mm expanded diameter) was used in all patients. The final choice of the prosthesis size was made according to guidelines [14], while the transfemoral or transapical approach was chosen on the basis of aorta and peripheral artery evaluation by MDCT.

Statistical Analysis

Statistical analysis was performed with the SPSS version 17.0 software (SPSS Inc., Chicago, Il). Continuous variables were expressed as mean±SD, and discrete variables were expressed as absolute numbers and percentages. The intra-observer and inter-observer variability for the evaluation of AoA-$DMax_{MDCT}$, AoA-$DMin_{MDCT}$ and AoA-A_{MDCT} were tested with Cohen's Kappa. Student *t* test was used to test differences of continuous variables between the baseline and post-TAVI parameters. Regarding AoA-D and Ao-A, the Spearman's correlation and Bland-Altman analysis were used to compare MDCT vs. TTE and TEE. Variables were included in a multivariate logistic regression. The receiver-operating characteristic curve for mismatch between prosthesis and AoA size evaluated by different imaging modalities (i.e., a plot of sensitivity against 1-specificity for each cut-off value) was plotted to measure the area under the curve expressed as c-value and to reach the best mismatch cut-off to predict PAR. P value <0.05 and C value >0.5 were considered statistically significant.

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Results

Clinical characteristics, echocardiography and MDCT findings of the study patients at baseline and after TAVI are summarized in Table 1. All patients had severe AS (indexed aortic valve area 0.38±0.09 cm^2/m^2). The preprocedure aortic regurgitation was scored as grade 0, 1, 2, 3 and 4 in 114 (75.5%), 23 (25.2%), 8 (5.3%), 5 (3.3%) and 0 (0%) patients, respectively. AoA-diameter and area measured by TTE and TEE were 21.14±1.94 mm, 22.04±1.94 mm, 353.82±64.57 mm^2 and 384.33±67.30 mm^2, respectively. AoA-maximum and minimum diamaters and AoA-area evaluated by

MDCT were 25.04±2.39 mm, 21.27±2.10 mm and 420.87±76.10 mm^2, respectively, with a low intra-observer and inter-observer variability (K: 0.95 and 0.94).

Table 1. Baseline characteristics of the study population.

Variables	Baseline	Post- TAVI	p-value
Clinical characteritics			
Number of patients, n	151		
Gender (male/female)	45/106		
Age (y), mean±SD	81.16±6.36		
BMI (Kg/m^2), mean±SD	25.63±4.71		
BSA (m^2), mean±SD	1.73±0.2		
Logistic Euroscore, mean±SD	20.8±10		
Echocardiographic characteristics			
EDV/BSA (mL/m^2), mean±SD	56.73±20.59	54.48±20.18	.05
ESV/BSA (mL/m^2), mean±SD	21.53±14.44	24.28±20.23	.03
EF (%), mean±SD	58.66±11.61	64.25±50.64	NS
Peak aortic gradient (mmHg)	87.17±21.36	21.70±7.41	.0001
Mean aortic gradient (mmHg)	53.70±14.40	11.69±4.39	.0001
Aortic valve area/BSA (cm^2/m^2)	0.38±0.09	1.30±0.33	.0001
Preprocedural aortic regurgitation (0-4)	0.39±0.89	0.38±0.63	NS
Pulmonary pressure (mmHg)	41.07±11.17	34.43±8.72	.0001
AoA-D_{TTE} (mm), mean±SD	21.14±1.94		
AoA-A_{TTE} (mm^2), mean±SD	353.82±64.57		
AoA-D_{TEE} (mm), mean±SD	22.04±1.94		
AoA-A_{TEE} (mm^2), mean±SD	384.33±67.30		
MDCT characteristics			
AoA-$DMax_{MDCT}$ (mm), mean±SD	25.04±2.39		
AoA-$DMin_{MDCT}$ (mm), mean±SD	21.27±2.10		
AoA-A_{MDCT} (mm^2), mean±SD	420.87±76.10		
Intraobserver variability	0.95		
Interobserver variability	0.94		
TAVI			
Transapical (23/26/29 mm), n	94 (44/46/4)		
Transfemoral (23/26/29 mm), n	57 (33/24/0)		
Mismatch			
AoA-A_{TTE} mismatch (mm^2), mean±SD	121.42±49.16*		
AoA-A_{TEE} mismatch (mm^2), mean±SD	90.91±50.28*		
AoA-A_{MDCT} mismatch (mm^2), mean±SD	−21.36±70.41		

AoA-AMDCT, AoA-A measured by MDCT; AoA-ATEE, AoA-A measured by TEE; AoA-DMaxMDCT, maximum AoA-D measured by MDCT; AoA-DMinMDCT, minimum AoA-D measured by MDCT; AoA-DTEE, AoA-D measured by TEE; BMI, body mass index; BSA, body surface area; NS, not significant. * P < .001 vs mismatch for AoA-A measured by MDCT

The Pearson's correlation and Bland-Altman analysis are shown in figure 2 and 3.

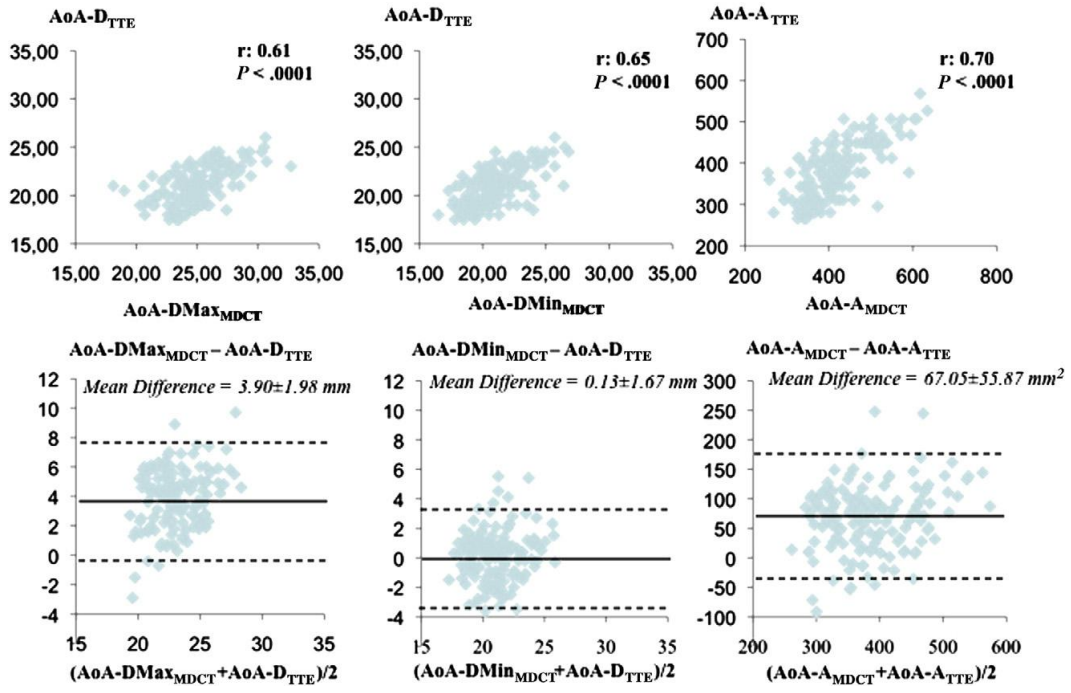

Figure 2. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between multidetector computed tomography (MDCT) and transthoracic echocardiography (TTE) assessment of aortic annulus diameter (AoA-D) and area (AoA-A). AoA-A_{MDCT}: aortic annulus area measured by MDCT; AoA-A_{TTE}: aortic annulus area measured by TTE; AoA-D_{TTE}: aortic annulus diameter measured by TTE; AoA-$DMax_{MDCT}$: maximum aortic annulus diameter measured by MDCT; AoA-$DMin_{MDCT}$: minimum aortic annulus diameter measured by MDCT.

TAVI was performed with a transfemoral or a transapical approach in 57 and 94 of them, respectively. A 23-mm Sapien valve was used in 77 (51%) patients, a 26-mm valve in 70 (46%) patients and a 29-mm valve in 4 (3%) patients, respectively. Procedural success was 100% without intra-operative mortality. After TAVI, peak and mean aortic gradients and pulmonary artery pressure decreased ($p<0.0001$) and aortic valve area increased ($p<0.0001$). The mismatch between the area of the implanted valve and the AoA-area measured by MDCT was lower than the mismatch between the AoA-area evaluated by TTE and TEE (-21.36±70.41 mm^2 versus 121.42±49.16 mm^2 and 90.91±50.28 mm^2, respectively, $p<0.01$).

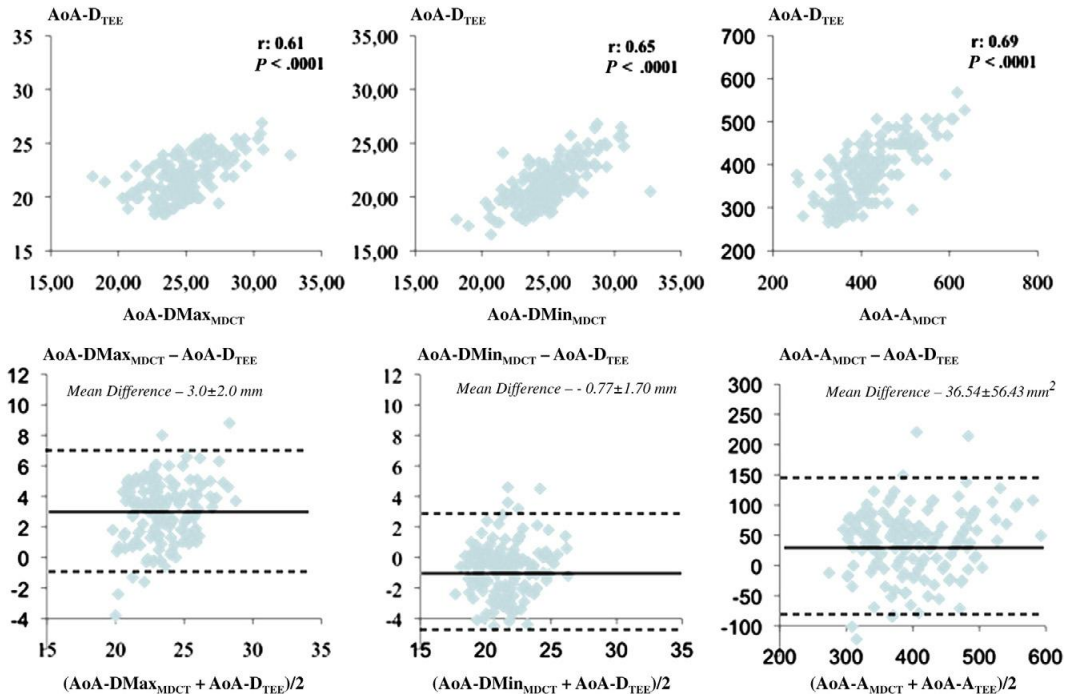

Figure 3. Pearson's correlation (upper panels) and Bland-Altman analysis (lower panel) between multidetector computed tomography (MDCT) and transesophageal echocardiography (TEE) assessment of aortic annulus diameter (AoA-D) and area (AoA-A). AoA-A_{MDCT}: aortic annulus area measured by MDCT; AoA-A_{TEE}: aortic annulus area measured by TEE; AoA-D_{TEE}: aortic annulus diameter measured by TEE; AoA-$DMax_{MDCT}$: maximum aortic annulus diameter measured by MDCT; AoA-$DMin_{MDCT}$: minimum aortic annulus diameter measured by MDCT.

Assessment of PAR showed no leakage in 58 (38%) patients, mild in 47 (31%) patients, mild to moderate in 26 (17%) patients, moderate to severe in 19 (13%) patients and severe in 1 (1%) patient immediately following valve implantation. At 30 days, 51 (34%), 54 (36%), 23 (15%), 22 (14%) and 1 (1%) patients showed PAR grade 0, 1, 2. 3 and 4, respectively. Therefore, significant PAR (≥2) occurred in 46 (30%) patients immediately after TAVI and at 30 days as well. According to the pre-TAVI intra-aortic regurgitation, a significant PAR (≥2) occurred in 27 (23.7%), 13 (56.5%), 2 (25%) and 4 (80%) patients with grade 0, 1, 2 and 3, respectively. As showed in Table 2, PAR was related to male sex (p=0.0005), high body mass index (p=0.05), higher pre-procedural aortic regurgitation (p=0.01),lower mismatch and cover index measured by MDCT (p=0.0093 and 0.0050, respectively). On the contrary, no difference was found in terms of cover index measured by TTE and TEE between patients with PAR<2 versus those with PAR ≥2.

Table 2. Determinants of postprocedural PAR.

Variables	AR < 2/4 (n = 105)	AR = 2/4 (n=46)	p-value	ROC (c value)
Clinical characteritics				
Male/female, n (%)	22 (21)/83 (79)	23 (50)/23 (50)	<0.01	0.65
Age (y), mean±SD	80.88±6.69	81.80±5.54	0.41	0.54
BMI (Kg/m^2), mean±SD	26.13±4.70	24.49±4.56	0.05	0.60
Echocardiographic characteristics				
EDV/BSA (mL/m^2), mean±SD	56.99±21.84	56.15±17.70	0.82	0.50
ESV/BSA (mL/m^2), mean±SD	20.64±13.96	23.50±15.40	0.28	0.59
EF (%), mean±SD	58.87±12.29	58.18±9.98	0.74	0.55
Peak aortic gradient (mmHg)	87.83±21.31	85.67±21.62	0.57	0.53
Mean aortic gradient (mmHg)	54.12±14.40	52.74±14.48	0.59	0.51
Aortic valve area/BSA (cm^2/m^2)	0.37±0.09	0.40±0.09	0.06	0.60
Preprocedural aortic regurgitation (0-4)	0.28±0.70	0.65±0.99	0.01	0.62
Pulmonary pressure (mmHg)	41.33±11.57	40.48±10.27	0.67	0.54
AoA-D_{TTE} (mm), mean±SD	21.01±1.94	21.45±1.89	0.20	0.57
AoA-A_{TTE} (mm^2), mean±SD	349.45±65.14	363.80±62.78	0.21	0.57
AoA-A_{TE} mismatch (mm^2), mean±SD	124.46±50.23	114.48±46.38	0.25	0.55
AoA-A_{TTE} cover index (%), mean±SD	26.19±9.82	23.88±9.53	0.18	0.57
AoA-D_{TEE} (mm), mean±SD	21.91±1.94	22.34±1.89	0.20	0.57
AoA-A_{TEE} (mm^2), mean±SD	379.77±67.89	394.73±65.46	0.21	0.57
AoA-A_{TEE} mismatch (mm^2), mean±SD	94.14±51.36	83.54±47.40	0.23	0.56
AoA-A_{TEE} cover index (%), mean±SD	19.72±10.28	17.34±9.97	0.19	0.56
MDCT characteristics				
AoA-$DMax_{MDCT}$ (mm), mean±SD	24.74±2.36	25.71±2.34	0.02	0.61
AoA-$DMax_{MDCT}$ mismatch (mm^2), mean±SD	−10.94±66.84	−45.13±73.30	0.01	0.62
AoA- $DMax_{MDCT}$ cover index (%), mean±SD	−2.43±14.26	−9.57±14.85	0.01	0.62
AoA-$DMin_{MDCT}$ (mm), mean±SD	21.08±2.08	21.70±2.08	0.10	0.59
AoA-$DMin_{MDCT}$ mismatch (mm^2), mean±SD	121.64±251.09	105.22±255.03	0.08	0.62
AoA- $DMin_{MDCT}$ cover index (%), mean±SD	25.71±10.48	21.94±10.78	0.05	0.63
AoA-A_{MDCT} (mm^2), mean±SD	412.21±75.49	440.61±74.55	0.04	0.62
AoA-A_{MDCT} mismatch (mm^2), mean±SD	61.69±49.73	37.67±51.01	0.01	0.65
AoA- A_{MDCT} cover index (%), mean±SD	13.00±10.3	7.7±10.39	<0.01	0.66
TAVI				
Transapical, n (%)	63 (60)	31 (67)		
Transfemoral, n (%)	42 (40)	15 (33)	0.39	

AoA-AMDCT, AoA-A measured by MDCT; AoA-ATEE, AoA-A measured by TEE; AoA-DMaxMDCT, maximum AoA-D measured by MDCT; AoA-DMinMDCT, minimum AoA-D measured by MDCT; AoA-DTEE, AoA-D measured by TEE; BMI, body mass index; BSA, body surface area; TAVI, transaortic valve implantation.

The best AoA-A_{MDCT} mismatch cut-off for predicting significant PAR was 61.5 mm^2 by receiver-operating curve, showing a better performance of MDCT versus TTE and TEE (c value= 0.65 versus 0.55 and 0.56, respectively) (Figure 4).

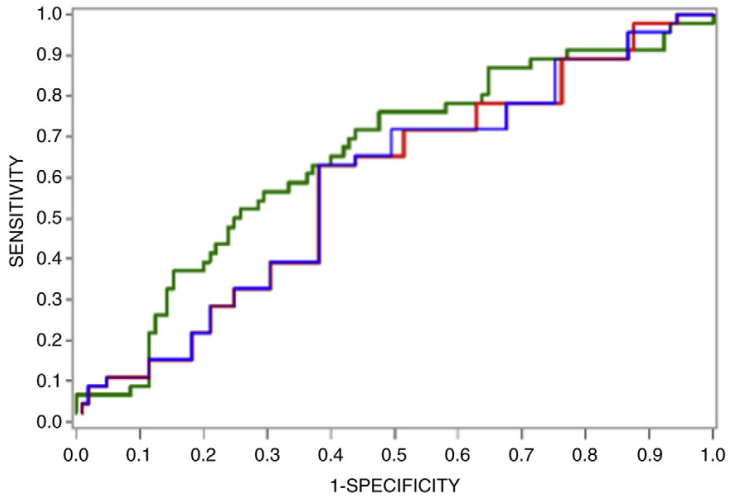

Figure 4. Receiver-operating curve (ROC) of predictive model for occurrence of post-procedural PAR using AoA-A_{MDCT} mismatch (green curve), AoA-A_{TTE} mismatch (blue curve) and AoA-A_{TEE} mismatch (red curve). AoA-A_{MDCT} mismatch showed the best prognostic power for predicting significant PAR with a cut-off value of 61.5 mm2 corresponding to a cover index of 13%.

Table 3 reports the distribution of significant PAR in comparison with the actual size of the valves implanted in the study patients, the valve sizes that in principle should have chosen based on TEE and MDCT and the number of patients with or without TEE and MDCT valve size matching. Theoretically, according to TEE criteria a 23-mm, 26-mm or 29-mm valve were chosen when AoA-diameter measured by TEE was between 18 and 21 mm, between 21 and 25 mm and >25 mm, respectively. According to MDCT criteria a 23-mm, 26-mm or 29-mm valve were chosen when AoA-area measured by MDCT was between 254 and 354 mm^2, between 354 and 469 mm^2, and between 469 and 599 mm^2, respectively. TEE and MDCT measurements were in agreement only in 71 out of 151 (47%) patients (Table 4).

It is noteworthy that a higher incidence of significant PAR was observed when a smaller prosthesis was implanted according to intra-procedural balloon sizing despite both TEE and MDCT indicated a larger prosthesis (7 out of 17 versus 9 out of 53 patients, $p<0.05$). A higher rate of significant PAR also occurred when a smaller prosthesis was implanted despite a larger AoA size was measured by MDCT as compared to that found with TEE (29 out of 65 patients versus 0 out of 8 patients, $p<0.01$).

Table 3. Number of patients with significant PAR, comparison between actual size of implanted valves and valve sizes that should have been chosen based on TEE and MDCT measurements, and number of patients with or without TEE-MDCT valve size matching

PAR=2	Size of implanted valves	Size based on AoA-D_{TEE}	Size based on A-A_{MDCT}	Patients(n)
3	23-mm valve	23	23	21
14	(n = 77 patients)	23	26	34
0		26	23	5
7		26	26	17
0	26-mm valve	23	23	1
0	(n = 70 patients)	23	26	6
1		26	23	2
6		26	26	30
15		26	29	31
0	29-mm valve	26	29	2
0	(n = 4 patients)	29	29	2

AoA-A_{MDCT}, AoA-A by MDCT; AoA-D_{TEE}, AoA diamter by TEE.

Table 4. Table 4. Relationship between prosthesis size indication by MDCT vs TEE, size of implanted prosthesis and number of patients with significant PAR.

MDCT vs TEE	Prosthesis size implanted	Patients, n, (%)	PAR ≥2 (n)
Agreement	Concordant	53(35)	9*
Agreement	Smaller	17(11)	7*
Agreement	Larger	1(1)	0
Oversizing of MDCT vs TE	Smaller (according to TEE)	65(43)	29†
Undersizing of MDCT vs TEE	Larger (according to TEE)	2(1)	1†
Oversizing of MDCT vs TEE	Larger (according to MDCT)	8(5)	0
Undersizing of MDCT vs TEE	Smaller(according to MDCT)	5(3)	0

* P < .05.;† P <.01.

Discussion

The main findings of our study are: a) the shape of the AoA is elliptical and not circular; b) there is a minimal difference between AoA-minimimum diamater measured by MDCT and both AoA-diameters evaluated by TTE and TEE, while a significant difference was found versus AoA-maximum diameter measured by MDCT in comparison with TTE and TEE; c) both TTE and TEE underestimate annulus size as compared to MDCT, likely because of the assumption that AoA has a circular shape; d) a mismatch of 61.5 mm^2 between prosthesis size and AoA-area measured by MDCT is a better predictor of PAR as compared to the mismatch between prosthesis size and TTE and TEE; e) as

compared to TEE, AoA assessment by MDCT may lead to implantation of a larger prosthesis in a sizable proportion of patients.

Detaint et al. [15] suggested that the occurrence of significant PAR is related to the lack of congruence between the annulus and the device. To appraise the congruence between annulus and device size, they used a "cover index" integrating aortic annulus and prosthesis diameters. The significant relationship between a low cover index and significant PAR suggests that a certain degree of prosthesis over sizing is needed to ensure good apposition of the prosthesis to the aortic annulus. Indeed, routine over sizing with prostheses 10–20% larger than the native annulus, as measured by TEE, and a trend to a lower valve positioning have been associated with a reduction of PAR rate. [16] A possible explanation of AoA size underestimation by echocardiography is the complexity of aortic root anatomy. This anatomic area is located between the basal attachment of the aortic valve leaflets within the left ventricle and their peripheral attachment at the level of the sinotubular junction describing the shape of a crown. [13] The AoA is defined as a virtual ring formed by joining the basal attachment points of the leaflets within the left ventricle of this crown-shaped structure. Of note, the virtual ring is elliptical in most cases. [13] Measurement of the aortic root by TTE and TEE is limited by the 2-dimensional nature of these imaging modalities. Indeed, TTE and TEE do not transect the full diameter of the outflow tract. On the contrary, they cut a tangent across the root, providing a measurement of the minimum diameter of the elliptical AoA only. This may be the main reason of true AoA area underestimation by echocardiography. Although prosthesis over sizing may limit PAR, overall this complication still occurs in 65% to 90% of patients, while a moderate-to-severe PAR has been reported in up to 20% of patients. [17] Abdel-Wahab et al. [18] recently demonstrated that even moderate PAR is associated with a higher incidence of heart failure and in-hospital mortality. On the other hand, inappropriate valve over sizing may result in redundancy of leaflet tissue leading to altered valve function and reduced durability and even annulus rupture [19]. Thus, a more accurate annulus sizing with 3-D techniques is desirable. Newer imaging modalities such as MDCT are emerging as reliable techniques because they allow precise measurement of the aortic root at any desired plane. Tops et al. [9] reported that the annulus has an oval configuration in approximately 50% of patients evaluated for TAVI, with a mean difference of 3.0±1.9 mm between coronal and sagittal measurements. Similarly, Delgado et al. [20] described an oval configuration of the annulus with a significant difference between the mean coronal and sagittal diameters. Recently, the annulus has been evaluated using a 3-chamber reconstruction that replicates the parasternal long-axis view obtained with TTE and TEE [21, 22] or using a double oblique transverse imaging orthogonal to the aortic root that incorporates the maximal and minimal diameter measurements of the basal ring below the

hinge point of the aortic valve cusps [23]. It is noteworthy that, regardless of the methods used, the absolute difference between MDCT and both TTE and TEE is greater than that between TEE and TTE. [22] In agreement with previous studies, all our patients showed an elliptical AoA shape with a mean difference of 3.77 mm between maximum and minimum diameters. Moreover, the difference between the maximum diameter measured with MDCT and those measured with TTE and TEE (3.90±1.98 mm and 3.2±2.0 mm, respectively) was significantly greater than the <1 mm difference found between TTE and TEE diameters. Differently from other studies, we measured the aortic annulus area by MDCT. This was done because the true maximum and minimum diameters are not located in sagittal and coronal planes as a rule and the aortic annulus orientation may change in each patient. Therefore, the area measurement may be more representative of the real annulus size rather than the diameter and may give a more appropriate assessment for choosing prostheses of correct size. Indeed, a 61.5 mm^2 cut-off was identified as a better predictor of significant PAR. Moreover, a larger prosthesis would have been chosen according to this cut-off value in 48% of the cases. Of note, patients with disagreement between MDCT and TEE measurements and underestimation of aortic annulus size with TEE had a higher incidence of significant PAR. These results are in agreement with a recent study demonstrating that MDCT modified TAVI strategy in a percentage ranging between 38 and 42. [22] Imaging assessment similar to MDCT may be obtained without radiation exposure using 3-D TEE or cardiac magnetic resonance. Ng et al. [24] demonstrated that 3-D TEE may overcome the geometric assumption limitation by allowing direct planimetry of the cross-sectional annular area. However, an underestimation of up to 9.6% as compared to MDCT was still found. This is likely due to a lower spatial resolution of 3-D TEE volumetric imaging and operator-dependance of this technique. Finally, data on cardiac magnetic resonance for the evaluation of patients undergoing TAVI are not available yet.

Limitations of the study

Several limitations are present in this study. First, as PAR was evaluated by echocardiography at the end of the procedure, the shortcomings of assessing eccentric jets by echocardiography have to be kept in mind. [25] Second, the incongruence between prosthesis and aortic annulus area was considered as the underlying cause of aortic regurgitation. However, several other mechanisms may be involved such as valvular damage during implantation, too low implantation of the valve and valve malapposition due to severe calcifications. However, all these conditions were ruled out in the unbiased analysis of the data. Third, patients with inadequate echocardiography window or impossibility to perform MDCT with ECG triggering were excluded from the present study.

Conclusions

This study shows that the lack of congruence between prosthesis and annulus size is associated with PAR. MDCT is a better tool for detecting the mismatch between prosthesis area and aortic annulus area and for predicting PAR as compared to TTE and TEE. An MDCT-based approach may be a reliable method to select the appropriate prosthesis size for TAVI. In this regard, specific MDCT-based sizing recommendations should be developed.

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Summary and Conclusion

Summary

The general introduction of the thesis outlines the characteristics and indications of TAVI, and the current and future role of cardiac imaging modalities (2D/3D TTE/TEE, MDCT, MRI) in the diagnostic process and for decision-making in this setting.

Chapter 1 illustrates the feasibility and accuracy of 3D TTE compared to 2D TTE and MDCT for the measurement of aortic annulus dimensions in the preoperatory evaluation of patients candidates to TAVI. 3D TTE evaluation was feasible in the majority of the patients with low intra and inter observer variability. 3D TTE and MDCT measurements did not differ significantly, with excellent agreement in the selection of cases with too small or too large annulus (recognized exclusion criteria for TAVI) while, as expected due to the oval shape of the aortic annulus, the 2D TTE annulus area, geometrically derived from 2D TTE diameter, was considerably lower in comparison both with 3DTTE and MDCT planimetric surface area. A good agreement in the choice of prosthetic size in cases scheduled for the procedure was found between the 3D TTE and MDCT. Subsequently, even though it's known that MDCT provides precise information about the annulus anatomy and remains the gold standard for the pre-operative assessment of TAVI candidates, 3D TTE may play a role in those patients that can't be studied by MDCT for several reasons such as impaired renal function, severe breathlessness, and arrhythmias. 3D TTE does not require breath-old and contrast infusion, may be obtained at the bedside, in more critical cases, and also in the presence of arrhythmias.

Chapter 2 shows that CMR, due to its multiplanar reformatting capabilities, allows accurate short-axis visualization of the aortic annulus and precise measurement of the virtual ring corresponding to the site of prosthesis deployment with high reproducibility and accuracy as compared to MDCT. Moreover, it can estimate the coronary ostia height and aortic valve leaflet dimensions that is a key step for patient selection and procedural planning in order to prevent coronary obstruction during TAVI.

In **Chapter 3** a large series of aortic patients was studied to evaluate the capability of 3D TEE to estimate preoperatively the distance between the aortic annulus and the left main ostium (AoA-LM), its accuracy in comparison with MDCT-derived measurements, the ability of the 3DTEE-derived

measurements in predicting the stent landing zone as defined by the overlap of the prosthesis with mitral leaflet.

The results demonstrated that 3D TEE may estimates the AoA-LM distance as an alternative technique to MDCT. Moreover, 3D TEE allows an immediate evaluation of the distance between the mitral leaflet and aortic prosthesis after the implantation. This measurement was feasible in most of the cases (90%) and also accurate. In fact the 3D TEE computed prosthesis was similar to the prosthetic nominal value. Pre and post 3D TEE data concerning the valve and prosthesis morphology and simultaneous real time evaluation of the aortic root including the LM coronary ostium give new insights regarding TAVI and its complications.

Chapter 4 suggests that intraoperative 2D and 3D TEE may allow the identification of predictors of significant PAR following successful TAVI. In particular, incomplete device expansion due to aortic valve calcifications is believed to be one of the contributing factors to PAR post-TAVI. In fact, heavily calcified native aortic valves may not allow a perfect apposition of the device along the annulus circumference. Our data show that the calcifications of the commissure between the right coronary and non-coronary cusp is related to significant post-procedural PAR. Moreover, the measurement of an “area cover index”, defined as the percentage difference between planimetered aortic annulus area and the nominal prosthesis area, should be considered during patient selection for TAVI. As a low “area cover index” predicts the development of significant post-procedural PAR, this index could be utilized as an additional parameter when choosing the prosthetic size in all those patients with borderline 2D TEE annulus size. Probably a certain degree of prosthetic oversizing is needed in order to minimize the development of significant PAR after the procedure.

Chapter 5 shows that, in accordance with previous results, the lack of congruence between prosthesis and annulus size is associated with significant PAR. MDCT is a valuable modality for detecting the mismatch between prosthesis area and aortic annulus area and for predicting PAR. In details, a mismatch of 61.5 mm^2 between prosthesis size and aortic annulus area measured by MDCT is a predictor of PAR.

Conclusions

TAVI is an invasive technique whose success depends on multidisciplinary team approach, where imaging fulfils a definite part. Initial experience with TAVI was based on 2D echocardiography measurements. There is now evidence that a 2D approach to the anatomy of the aortic valve

apparatus is inadequate. Advanced cardiac imaging modalities, 3D echocardiography, MDCT and MRI, besides standard 2D echocardiography and angiography, play a crucial role in the diagnostic process and management of patients, allowing proper selection and planning, optimizing the procedure and increasing TAVI success. Echocardiography is the cornerstone of pre-procedure evaluation, complemented by MDCT. Both 3D TTE/TEE and MDCT have a higher predictive value for PAR than 2D echo measurements and have been shown to change valve sizing strategy compared with 2D echo. During TAVI, 2D, and particularly 3D, TEE can be used for guidance and, allowing the visualization of the left main ostium and the measurements of its distance from the annulus, increases the procedure safety.

In the future, as patients undergoing TAVI might be younger, CMR might gain significance by the absence of radiation issues.