Utility of conventional aortic root shot angiography for SAPIEN 3 prosthesis sizing in TAVI – feasibility and inter-reader variability

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Abstract

Objectives

We aimed to investigate whether conventional aortic root angiography (CA) alone can reliably facilitate valve selection, and to describe its inter-reader variability.

Background

The gold standard approach to prosthesis sizing before transcatheter aortic valve implantation (TAVI) is multi-slice computed tomography (MSCT).

Methods

Five TAVI specialists (three interventional cardiologists and two cardiac surgeons) independently reviewed pre-procedural CAs for 50 patients implanted with the Edwards SAPIEN 3 valve.

Results

The prosthesis size selected based on visual CA appraisal matched that based on MSCT in 60% of cases (range: 50–68%), with undersizing in 11% (4–33%) and oversizing in 29% (10–46%; p=0.187 for equality of proportions test). Agreement between CA-based and MSCT-based valve selection was moderate (K=0.41; Kw=0.61). Reassessment of choice following awareness of the annulus long-axis diameter did not significantly improve this agreement (0.40 and 0.63, respectively), though more undersizing (14%) and less oversizing (25%) occurred. Correct valve selection was more common in interventional cardiologists than cardiac surgeons (66% vs. 53%; p=0.0391), who made more oversizing errors.

Conclusions

There is modest agreement between CA-based and MSCT-based SAPIEN 3 selection. While the former should not be performed routinely, it may be informative in settings where MSCT and transesophageal echocardiography are unavailable.
Background

In aortic stenosis (AS) patients undergoing transcatheter aortic valve implantation (TAVI), erroneous estimation of annulus parameters leading to over/undersizing of the transcatheter heart valve (THV) can result in serious consequences [1]. These include annular rupture [2], conduction disorders [3], incomplete prosthesis expansion, prosthesis embolization [4], and a greater degree of residual paravalvular leak (PVL) [5, 6]. Consequently, accurate pre-procedural sizing is crucial.

Until 2010, transesophageal echocardiography (TEE) was the most commonly used imaging modality for THV size selection. However, over time it has been gradually replaced by multi-slice computed tomography (MSCT) [7]. The latter multiplanar imaging technique is now the gold standard for pre-procedural assessment of aortic root anatomy, used to determine the form and dimensions of the annulus, its distance from the coronary ostia, the burden and distribution of calcified residues, and AV cuspidity [8, 9]. While it is true that MSCT has improved the accuracy of long- and short-axis annular diameter estimations [8-14], particularly in the case of highly calcified valves [15], it also exposes the patient to harmful radiation and requires the use of contrast agent, limiting its application in patients with renal comorbidity [1, 7, 16, 17]. Furthermore, due to its high cost, MSCT may not be available in low-resource settings. For these reasons, it is useful to assess the utility of alternative imaging techniques for valve sizing in TAVI.

Conventional 2D angiography (CA) of the aortic root is routinely carried out during the TAVI procedure [18]. First proposed as an aid to valve sizing in surgical aortic valve (AV) replacement by Mukharji [19], this well-established imaging modality is low-cost and requires lower radiation and contrast agent doses compared to MSCT. To the best of our knowledge, THV selection based solely on appraisal of a CA aortic root shot has not been compared to the gold standard MSCT-based selection. In the present analysis, we aim to
ascertain whether reliable TAVI prosthesis sizing is possible based on such CA appraisal alone, and to describe the corresponding inter-reader variability.

Methods

The present study was a retrospective analysis of patients that underwent TAVI at the Augsburg-Schwaben Heart centre (Augsburg Hospital, Germany) between October 2016 and March 2017. The research was approved by the local ethics committee and conducted in line with the declaration of Helsinki. Written informed consent was unnecessary as existing anonymised data were utilised.

Only patients that underwent TAVI with the Edwards SAPIEN 3 THV were included in the study. The presence of a bicuspid AV or AV bioprosthesis resulted in exclusion.

Prior to TAVI, each patient underwent prospective ECG-gated multi-slice computed tomography (MSCT) with high-pitch spiral acquisition, using a third-generation, dual-source computed tomography scanner (Somatom Force; Siemens Healthcare, Germany).

The following settings applied: 250 ms gantry rotation; 66 ms temporal resolution; 2×196×0.6 collimation; a 120 kV tube voltage; and a 350 –500 mA tube current. Scan direction was cranio-caudal, extending from above the aortic arch to below the hip. Image acquisition was optimized for the left main coronary artery at 60% of the R–R interval. Contrast agent transit time was measured using the test bolus technique (10 mL of contrast agent followed by a 50 mL saline flush, both administered at a flow rate of 5 mL/s). For MSCT angiography, 50 mL of contrast agent (350 mg iodine/mL; Imeron, Bracco) were injected into an antecubital vein at a flow rate of 5 mL/s, followed by a 60 mL flush consisting of 80% saline and 20% contrast agent. Images were reconstructed using i26f kernel, with a slice thickness of 0.75 mm and an increment of 0.5 mm.
For precise determination of the aortic annulus plane, the lowest insertion points of the right, non-coronary, and left aortic cusp were aligned by stepwise manipulation of multiplanar reconstructions (Figure 1). The resulting scan was used to calculate aortic annulus parameters and to determine the most appropriate THV size. MSCT image analysis was performed by a cardiologist with several years of cardiac CT experience (Level 3) using Agfa Impax software.

Conventional root shot angiography (CA) using the Artis zee system (Siemens Healthcare, Germany) was also performed in each patient prior to THV implantation. This examination included an aortic root shot angiogram (10° left anterior oblique, 10° cranial view) obtained using 10 mL of contrast agent (Iomeprol 350 mg/mL; Imeron 350, Bracco) injected into the right aortic cusp via a 5F curved pigtail catheter. Precise determination of the perpendicular annulus plane was achieved according to the ‘follow the right cusp’ rule [20].

Following TAVI completion, all pre-procedural CA aortic root shots were retrospectively reviewed by five experienced readers (two cardiac surgeons [R1 and R2] and three interventional cardiologists [R3–R5]). Each reader independently estimated the appropriate SAPIEN 3 valve size (20, 23, 26, or 29 mm) based on visual CA image appraisal alone (Figures 2A and 2C). Subsequently, the long-axis diameter of the elliptically shaped AV annulus (“annular long-axis diameter”) was measured from hinge point to hinge point of the AV cusps (Figure 2B and 2D) and each reader reassessed their selection based on this additional information.

TAVI was performed in the catheterisation laboratory by the resident Heart Team at our institution, consisting of interventional cardiologists and cardiac surgeons. In all patients, the procedure was carried out under conscious sedation with balloon aortic valvuloplasty (BAV) pre-dilation. Balloon post-dilation was performed in the case of treatable residual
PVL. At least one additional aortogram was acquired following prosthesis implantation. Categorical data are presented as absolute values and proportions. Inter-reader agreement was assessed using Cohen's kappa coefficient, expressed as both unweighted kappa (K) and weighted kappa (Kw), the latter of which also considers the magnitude of the deviation. A Hotelling's T square test was used to determine the statistical significance of agreements over all raters. Any difference in the rate of correct valve sizing between physicians was identified using a test for equality of proportions. All statistical analyses were performed using R version 3.4.2, with a p-value of <0.05 considered significant.

Results

In total, 50 TAVI patients met the study criteria and had both an MSCT and CA aortic root shot available for evaluation. MSCT assessment prior to TAVI resulted in the implantation of a 20 mm valve in one patient (2%), a 23 mm valve in 23 patients (46%), a 26 mm valve in 16 patients (32%), and a 29 mm valve in 10 patients (20%). The agreement between visual CA-based valve selection (without knowledge of the annular long-axis diameter) and MSCT-based valve selection was moderate (K = 0.41; Kw = 0.61) (Figure 3A). On average, valve selection based on the two imaging methods matched in 60% of cases, with CA appraisal resulting in relative undersizing in 11% and oversizing in 29% of cases; however, these proportions varied substantially across individual readers (range: 50–68%, 4–22% and 10–46%, respectively) (Figure 4A). Using the CA-based approach, R4 and R5 demonstrated the highest degree of agreement with MSCT-determined valve sizes, followed by R3, R2 and R1 (K = 0.52, 0.51, 0.42 and 0.31, respectively), with a test for equality of proportions resulting in a non-significant p-value of 0.37 (Table 1A). In all cases, Kw was higher than K, with the same trend seen across raters (Kw = 0.73, 0.73, 0.63, 0.50 and 0.47, respectively; p = 0.15). An inter-rater matrix...
comparison of K and Kw revealed there to be no statistically significant differences (Table 2).

Overall, knowledge of the annular long-axis diameter did not result in a significantly greater agreement between CA-based and MSCT-based valve size selection (K = 0.40 vs. 0.41, p = 0.951; Kw = 0.63 vs. 0.61, p = 0.753) (Figure 3B). Accordingly, there was very little change in the rate of correct valve sizing (mean: 61% vs. 60%; p = 0.86), though more undersizing (mean: 14% vs. 11%; p = 0.35) and less oversizing (mean: 25% vs. 28%; p = 0.36) occurred (Figure 4B).

Awareness of the annular long-axis diameter resulted in an increase in K for two readers (R5: from 0.52 to 0.56 and R1: from 0.28 to 0.32) and a decrease for the other three (R4: 0.51 to 0.48; R3: 0.42 to 0.39; and R2: 0.31 to 0.28) (Table 1). A test for equality of proportions resulted in a non-significant p-value of 0.214. Kw was again greater than K in all readers, being highest for R5, followed by R4, R3, R1 and R2 (0.77, 0.74, 0.62, 0.54 and 0.47, respectively).

Overall, the proportion of correctly sized valves was higher when the CA aortic root shot was read by interventional cardiologists compared to cardiac surgeons, regardless of whether annular long-axis diameter was known (66% vs. 53%; p = 0.0391) or unknown (66% vs. 52%; p = 0.0177) (Figure 5). Both cardiac surgeons (R1 and R2) were more accurate than their interventional cardiologist counterparts (R3, R4 and R5) when visually judging the need for larger valve sizes, while the inverse was true for intermediate-sized valves (Table 1A). Additionally, cardiac surgeons less commonly made undersizing errors based on visual CA appraisal, but more commonly made oversizing errors (Figure 4A).

However, these unbalances became notably less pronounced when the annular long-axis diameter was known (Table 1B).

Discussion
The present analysis suggests that CA aortic root shot appraisal results in only modestly accurate prosthesis sizing, as compared to the gold standard MSCT reference size. Furthermore, CA-based quantification of the annular long-axis diameter did not improve the overall accuracy of valve size selection. As such, CA-based THV sizing should not routinely replace its MSCT-based counterpart. Inter-reader variability was modest, with the interventional cardiologists in our small study generally making more appropriate selections than the cardiac surgeons.

On average, 60% of valves were correctly sized based on the CA aortic root shot, with fair-to-moderate agreement between CA-guided and MSCT-guided selections [21]. While this does not appear to be particularly promising at first glance, it is also important to consider the degree of inaccuracy, with severe over/undersizing resulting in a greater likelihood of complications [22]. When the magnitude of each discrepancy was taken into account by K weighting, moderate-to-substantial agreement was achieved [21], suggesting that inaccuracies were largely small. This is further demonstrated by the fact that only 3% of CA-guided valve selections were ≥ 1 size away from their MSCT-guided counterparts. Furthermore, the majority of inaccuracies led to oversizing rather than undersizing errors.

This is significant given that moderate oversizing (5–15% for the SAPIEN 3) has been shown to be protective against post-procedural PVL [23], while undersizing has no clinical utility and results in incomplete apposition to the native aortic annulus [24]. In addition, several common oversizing-related complications, such as conduction abnormalities, do not necessarily translate into poorer outcomes [25, 26], while PVL, the most common undersizing-related complication, has been highlighted as an independent risk factor for post-procedural mortality [24]. Nevertheless, the advantage of slight oversizing was likely
already accounted in MSCT-based valve selection, meaning that the oversizing observed with CA-based valve selection would be more severe than it first appears. This is concerning, given that severe oversizing of balloon-expandable valves has been associated with a higher risk of aortic root rupture [2], a rare (0.5–1%) but often fatal TAVI complication [27].

While the above findings suggest that CA-based THV sizing is not an appropriate substitute for the MSCT gold standard in routine clinical practise, they demonstrate it to provide a reasonable approximation of size requirements, with only a small, non-significant degree of inter-rater variation. As such, it may be useful to guide valve selection in low-resource settings where access to MSCT or TEE technology is limited. Furthermore, given that only a fraction of the contrast agent used for MSCT was required for CA, the latter approach may be an interesting alternative for patients at high risk of contrast-induced nephropathy [28]. As always, a balance must be struck between the risks and benefits of each technique.

In general, knowledge of the annular long-axis diameter did not result in a significantly greater agreement between CA-based and MSCT-based valve size selection. Accordingly, there was very little change in the rate of correct valve sizing, though a general trend towards more undersizing and less oversizing emerged. This effect is likely related to the elliptical conformation of the AV annulus. While MSCT allows calculation of a mean annulus diameter based on measurements of both the short and long axis, with motion-induced artefacts circumvented through gated imaging [29], 2D CA provides data only for the annular long-axis, which must then be used to approximate the overall annulus diameter, with no compensation for movement. The present data suggest that, upon receipt of the long-axis measurements, physicians may tend towards underestimation of the short-axis diameter and selected a smaller THV to compensate. Had this approach
been used for valve selection in real life, the result would likely have been greater PVL, poorer transvalvular gradients and less scope for functional improvement [5, 6]. Physician perception seems also to play a role, with the accuracy of two readers improving and that of three readers declining when long-axis data was made available; however, these changes were small. Thus, it may be concluded that measurement of the aortic annulus long-axis diameter provides little-to-no clinical advantage in CA-based THV sizing, and would prolong interventional times.

Overall, the proportion of correctly sized valves was higher when the CA was read by interventional cardiologists than by cardiac surgeons, regardless of whether annular long-axis diameter was known or unknown. This highlights the importance of exploiting the particular expertise and speciality of certain Heart Team members in TAVI, with interventional cardiologists typically having more experience in the appraisal of angiography images [30]. Indeed, cardiac surgeons often play a more supportive role in contemporary TAVI at well-established institutions, stepping in in the case of procedural complications [31]. However, based on visual CA appraisal alone, both cardiac surgeons in the present study were more accurate than their interventional cardiologist counterparts in judging the need for larger valve sizes, less frequently making undersizing errors. In contrast, oversizing errors were less commonly made by interventional cardiologists. This highlights the value of the guideline-recommended multidisciplinary Heart Team in TAVI [8]; indeed, it would be interesting to explore whether a collaborative effort towards CA-based valve sizing involving multiple members of the Heart Team would improve the accuracy of valve selection.

The principle limitation of the present study was the small number of readers included, becoming even more relevant when comparing the different types of cardiac specialists. Larger-scale studies would be informative. Furthermore, all readers are current
practitioners at the same TAVI-proficient site, meaning that the agreement between them may be higher due to workplace and geographical influences. As such, the present findings cannot be generalised to other institutions and cardiologists with different levels of TAVI experience. The use of one model of THV, the balloon-expandable SAPIEN 3, also limits the generalisation of results to patients undergoing TAVI with other valve types, particularly self-expanding prostheses. Finally, the assumption that CA-based valve selection was accurate when it matched that indicated by MSCT-based sizing may be misplaced, given that sizing errors are still possible even when using the gold standard approach. Unfortunately, data on real-world valve under/over-sizing at implantation was not available to corroborate MSCT-based selection in the present study.

CONCLUSION

There is only moderate agreement between the THV selection made based on CA aortic root shot assessment and that made using the gold-standard MSCT approach. As such, CA should not be routinely used for the purpose of valve sizing in resource-rich settings. Nevertheless, it may be a reasonable approach in the case that MSCT or TEE is unavailable, particularly given that it is already a routine step in the TAVI procedure. In the case that the CA-based approach is employed, the judgement of an interventional cardiologist may be particularly useful for maximising accuracy, while the supplementary view of a cardiac surgeon may help to minimise undersizing. However, any time CA based valve selection is utilized balloon sizing prior to implantation is mandatory to further improve accuracy. Further studies in a larger sample and range of readers would be informative.

List Of Abbreviations
AS Aortic stenosis
BAV balloon aortic valvuloplasty
CA conventional aortic root angiography
K unweighted kappa
Kw weighted kappa
MSCT multi-slice computed tomography
PVL paravalvular leak
TAVI transcatheter aortic valve implantation
TEE transesophageal echocardiography
THV transcatheter heart valve

Declarations

Ethics approval and consent to participate
The research was approved by the Augsburg University ethics committee and conducted in line with the declaration of Helsinki. Written informed consent was unnecessary as existing anonymised data were utilised.

Consent for publication
Not applicable.

Availability of data and material
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest
Stephan Krapf is a consultant for Jena Valve and Edwards Lifesciences, Christian Thilo is a consultant for Boston Scientific and receives research support from Edwards Lifesciences
and Boston Scientific, Peter Bramlage is a consultant for Boston Scientific and Edwards Lifesciences. The other authors have no conflict of interest to disclose.

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**Authors` contributions**

LG and CT contributed to conception and design of this work. LG, SK, Foe, TMH, WvS and CT collected the data. BU designed the statistical approach, analysis, and interpretation. PB outlined the first version of the manuscript, which all other authors revised for important intellectual content. All authors approved the final version of the manuscript to be submitted.

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## Tables

**Table 1:** Number of correct reader assessments when the annular long-axis diameter is unknown (A) and known (B)

|                | Cardiac surgeons | Interventional cardiologists |
|----------------|------------------|-----------------------------|
|                | R1   | R2   | R3   | R4   |                |
| (A) Unaware of annular long-axis diameter |       |       |       |       |                |
| 20 mm (n/N [%]) | 0/1  | 0/1  | 0/1  | 0/1  | 0,              |
| 23 mm (n/N [%]) | 8/23 | 7/23 | 14/23| 15/23| 18/,           |
| 26 mm (n/N [%]) | 9/16 | 10/16| 11/16| 13/16| 10/,           |
| 29 mm (n/N [%]) | 8/10 | 9/10 | 6/10 | 6/10 | 6/1,           |
| K (95% CI)          | 0.28 | 0.31 | 0.42 | 0.51 | (0.28–0.66)    |
| Kw (95% CI)         | 0.47 | 0.50 | 0.63 | 0.73 | (0.32–0.68)    |
| (B) Aware of annular long-axis diameter |       |       |       |       |                |
| 20 mm (n/N [%]) | 0/1  | 0/1  | 0/1  | 0/1  | 0,              |
| 23 mm (n/N [%]) | 10/23| 10/23| 14/23| 12/23| 20/,           |
| 26 mm (n/N [%]) | 10/16| 9/16 | 10/16| 13/16| 10/,           |
| 29 mm (n/N [%]) | 7/10 | 6/10 | 6/10 | 7/10 | 6/1,           |
| K (95% CI)          | 0.32 | 0.28 | 0.39 | 0.48 | (0.35–0.73)    |
| Kw (95% CI)         | 0.54 | 0.47 | 0.62 | 0.74 | (0.27–0.66)    |

*Legend:* K, kappa; Kw, weighted kappa; CI, confidence interval.

**Table 2:** K comparison using z-test***
|                | Cardiac surgeons |                | Interventional cardiologists |
|----------------|------------------|----------------|-------------------------------|
|                | R1   | R2   | R3   | R4   | R1   | R2   | R3   | R4   |
| Cardiac        |      |      |      |      |      |      |      |      |
|                |      |      |      |      |      |      |      |      |
| surgeons       |      |      |      |      |      |      |      |      |
| R1             |      |      |      |      |      |      |      |      |
| R2             |      | 0.831** |      | 0.425* | 0.143* |      |      |      |
| Interventionsal|      |      |      |      |      |      |      |      |
| cardiologists  |      |      |      |      |      |      |      |      |
| R3             |      | 0.243** | 0.336** |      | 0.531* |      |      |      |
| R4             |      | 0.061** | 0.096** | 0.510** |      |      |      |      |
| R5             |      | 0.053** | 0.086** | 0.489** | 0.984** |      |      |      |

Legend: K, kappa. *unweighted kappa; ** weighed kappa; p-values based on z-test; *** for valve selection based on CA aortic root shot appraisal without knowledge of the annular long-axis diameter.

Figures
Figure 1

MSCT-based valve sizing approach Legend: MSCT, multi-slice computed
tomography. Example MSCT-based images from a 81-year-old female with
implantation of a 23 mm SAPIEN 3 valve. Sagittal (A) and coronal (B) multiplanar
reformats (MPR) displaying short and long annulus diameters, respectively (mean
diameter of 23.1 mm \([21.9 + 24.3 \text{ mm}/2]\)). The corresponding transverse MPR is
shown in C.
Figure 2

AC-based valve sizing approach Legend: AC, conventional aortic root angiography. Example conventional root shot angiography images for visual appraisal (A and C), with subsequent measurement of the long-axis diameter of the aortic valve annulus (distance from hinge point to hinge point of the AV cusps; shown by white arrow in B and D). Upper panel: 85-year-old female with an
MSCT-based mean AV diameter of 22.3 mm and implantation of a 23 mm SAPIEN 3 valve. Lower panel: 86-year-old male with an MSCT-based mean diameter of 28.5 mm and implantation of a 29 mm SAPIEN 3 valve.

Figure 3

Agreement between AC-based and MSCT-based valve size selection when annular long-axis diameter is unknown (A) or known (B) Legend: CA: conventional aortic root angiography; K, kappa; Kw, weighted kappa; MSCT, multi-slice computed tomography. A) K = 0.41, Kw = 0.61. B) K = 0.40, Kw = 0.63. P = 0.951 for the comparison between A) K and B) K; P = 0.743 for the comparison between A) Kw and B) Kw.
Figure 4
Proportion of correctly sized/undersized/oversized valves based on CA appraisal without (A) and with (B) awareness of the annular long-axis diameter Legend: CA, conventional aortic root angiography; R, reader. “Correct” valve size is defined as that selected based on pre-procedural MSCT.

Figure 5
Comparison of the accuracy of CA-based valve selection between cardiac surgeons and interventional cardiologists with and without awareness of the annular long-axis diameter Legend: CA, conventional aortic root angiography.