Aortic valve and left ventricular outflow tract calcium volume and distribution in transcatheter aortic valve replacement: Influence on the risk of significant paravalvular regurgitation

Nicolaj C. Hansson a,*, Jonathon Leipsic b, Francesca Pugliese c, Henning R. Andersen a, Alexia Rossi c, Matheus Simonato b, Kaare T. Jensen a, Evald H. Christiansen a, Christian J. Terkelsen a, Philipp Blanke b, Mariann Tang d, Lars R. Krusell a, Kaj-Erik Klaaborg d, Kim Terp d, Simon Kennon e, Danny Dvir b, Hans Erik Bøtker a, John Webb b, Bjarne L. Nørgaard a

a Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
b Department of Medical Imaging and Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada
c Centre for Advanced Cardiovascular Imaging, NIHR Cardiovascular Biomedical Research Unit at Barts, Barts and the London School of Medicine, Queen Mary University
of London, London, UK
d Department of Cardiothoracic Surgery, Aarhus University Hospital, Aarhus, Denmark
e Department of Cardiology, London Chest Hospital, London, UK

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Corresponding author: NC Hansson
Department of Cardiology, Aarhus University Hospital Skejby, Palle Juul-Jensens Boulevard 99, 8200 Aarhus N, Denmark.
E-mail address: nh@dadlnet.dk (N.C. Hansson).

Abstract

Objectives: We sought to determine the impact of aortic root calcium on the risk of significant paravalvular regurgitation (sPAR) in transcatheter aortic valve replacement (TAVR).

Methods: In 302 consecutive patients from 3 centers, aortic root calcium was quantified volumetrically on pre-TAVR multidetector computed tomography (MDCT) in three regions: 1) the aortic valve region, 2) the overall left ventricular outflow tract (LVOT) and 3) the upper LVOT. Transcathether heart valve (THV) oversizing was calculated as (THV nominal area/MDCT annular area−1)°—100. The study endpoint sPAR was a composite of post-dilatation (PD) and PAR > mild.

Results: sPAR occurred in 15% (46/302) of patients. Upper LVOT calcium volume was more predictive of sPAR than overall LVOT calcium volume, with an area under the receiver operating curve (AUC) (95% confidence interval [CI]) of 0.80 (0.67–0.89) vs. 0.60 (0.51–0.70); p=0.0001. The optimal cut-off calcium volume thresholds determined from receiver operating curves were 21mm3 and 30mm3 for upper LVOT and overall LVOT calcium, respectively. Upper LVOT calcium ≥ 21mm3, but not overall LVOT calcium ≥ 30mm3, independently predicted sPAR, odds ratio (95%CI): 9.5 (4.1–22.3) vs 1.6 (0.6–2.7). Upper LVOT calcium was more predictive of sPAR in patients with THV oversizing ≥ 13% compared to patients with THV oversizing<13%, AUC (95% CI): 0.83 (0.72–0.93) vs. 0.67 (0.51–0.74); p < 0.0001.

Conclusions: Upper LVOT calcium predicts more-than-mild paravalvular regurgitation following TAVR or the need for postdilatation. Upper LVOT calcium is most predictive of paravalvular regurgitation in the event of THV oversizing ≥ 13%.

1. Introduction

Post-procedural paravalvular regurgitation (PAR) remains a significant limitation in transcatheter aortic valve replacement (TAVR) and is associated with increased mortality.[1] Potential future broadening of TAVR indications to lower-risk patients calls for further improvement in procedural outcomes. Appropriate transcatheter heart valve (THV) sizing relative to the aortic annulus is crucial to secure anchoring and prevent PAR without increasing the risk of aortic root injury.[1–4] Contrast-enhanced multidetector CT (MDCT) has emerged to play a key role in TAVR planning.[5] Indeed, introduction of an MDCT-based THV sizing algorithm has been shown to reduce the risk of PAR.[6] In addition to the assessment of annular dimensions, MDCT allows for detailed assessment of aortic root and left ventricular outflow tract calcium (LVOT) calcification. Through detailed quantitative calcium analysis it has recently been demonstrated that the distribution and amount of calcium in the aortic root and LVOT have implications for the risk of aortic root injury.[3] Moreover, calcium may prevent apposition of the THV device to the aortic wall, thus creating a nidus for PAR.[7,8] The majority of previous studies addressing the implications of MDCT-based calcium evaluation for PAR have been limited by single-center design, small cohort size and lack of standardized methodology for calcium quantification.[7–16] In addition, the interplay between aortic root calcium and THV sizing for the risk of PAR is not fully understood. Thus, the objective of this multicenter study was to determine the implication of calcium volume and distribution for PAR > mild and need for post-dilatation using a novel calcium quantification methodology.

2. Methods

2.1. Study population and TAVR procedure

324 consecutive patients who underwent pre-TAVR MDCT and TAVR at 3 institutions (Aarhus University Hospital, Aarhus, Denmark, n=187; St Paul's Hospital, Vancouver, Canada, n=69 and London Chest Hospital, London, UK, n=68) between August 2011 and February 2014 were evaluated for inclusion in this observational study. TAVR was performed with the balloon-expandable Sapien XT transcatheter heart valve (THV; Edwards Lifesciences, Irvine, CA) according to standard practice.[17–19] THV size selection was based on MDCT analysis performed at each participating center.[20] Immediately after THV deployment PAR was evaluated by TEE and/or angiography. Postdilatation was performed in the event of PAR > mild using the same balloon volume as for THV implantation or with an additional 1–2 cc at the discretion of the treating physician.

2.2. CT image acquisition

As part of routine clinical practice, all patients underwent contrast enhanced MDCT scans in the craniocaudal direction with retrospective ECG-gating. MDCT protocols were applied according to each centers' standard practice. Scans were performed on either a 64-slice Discovery HD 750 high-definition scanner (GE Healthcare, Milwaukee, WI) with a scanner detector collimation width of 0.625 mm, detector coverage of 40 mm, gantry rotation time of 0.35 s, and scan pitch of 0.16–0.20 (adjusted per heart rate), or a Siemens Somatom Definition Flash Dual-Source scanner (Siemens Healthcare, Erlangen, Germany) with a 128°—0.625mm collimation, z-flying spot, gantry rotation time of 0.28 s, and scan pitch of 0.20–0.40 (depending on heart rate).[21]

2.3. MDCT image analysis

For the purpose of this study, all images were transferred to a core lab (Aarhus University Hospital, Denmark) after the TAVR procedure and post-processed offline using dedicated TAVR planning software (3mensio Structural Heart, 3mensio Medical Imaging BV, Bilthoven, the Netherlands).[3] All analyses was performed by one experienced TAVR MDCT reader in a blinded fashion without knowledge regarding patient characteristics, the TAVR procedure, echocardiographic data or clinical outcomes. Aortic root dimensions were determined as outlined in the supplementary data. As previously described,[3] calcium was quantified using patientspecific detection threshold in three specific regions (Fig. 1): 1. The overall LVOT (from the aortic annulus plane and 10mm into the left ventricle), 2. The upper LVOT (from the aortic annulus plane and 2mm into the left ventricle) and 3. The aortic valve region (from the aortic annulus plane to the left

coronary ostia) (see also supplementary data). The distal boundary of the upper LVOT region (ie, 2mm into the left ventricle) was chosen based on previously reported distances from the lower rim of the THV to the aortic annulus in order to include the calcium that would be in direct contact with the THV device.[22,23] In patients with calcium in the upper LVOT, the protrusion of annular calcium nodules into the lumen was evaluated. The severity of calcium lumen protrusion was assessed by relating the calcium nodule long-axis dimension to the corresponding annulus diameter (Fig. 1).

2.4. Echocardiographic assessment
All pre-discharge TTEs were retrospectively reviewed by 1 of 2 cardiologists with>4 years experience in post-TAVR echocardiography blinded to THV size, pre-TAVR echocardiographic and MDCT data. PAR was graded as mild, moderate or severe according to the Valve Academic Research Consortium-2 criteria.[24] THV function was assessed by determining the mean trans-THV gradient and effective orifice area (EOA).

2.5. Study endpoints
The study endpoint was a composite of postdilatation (as a surrogate of procedural PAR > mild) and/or PAR > mild at discharge. This composite endpoint is designated "significant PAR" (sPAR). Data on survival and all-cause mortality were collected from dedicated TAVR registries and patient records.

2.6. Statistical analysis
Continuous parametric variables are presented as mean ± SD and compared using the Students t-test. Continuous nonparametric variables are presented as median [interquartile range] and compared using the Mann-Whitney-U test. Categorical variables are presented as frequencies (percentages) and compared using Fisher's exact test or chisquare as appropriate. Non-parametric receiver operating curve (ROC) analysis was performed in order to test the discriminatory power of calcium volumes stratified by region, annular calcium protrusion and THV oversizing for prediction of the combined endpoint, sPAR. Area under the curves (AUCs) were compared using the method of DeLong et al.[25] The optimal cut-off points maximizing the sum of sensitivity and specificity were derived from the ROC curves. Multivariable logistic regression analysis was performed to determine the predictive value for sPAR of an upper LVOT/overall LVOT calcium volume, as well as annular calcium protrusion, above the optimal cut-off point. Adjusting was performed for the optimal degree of THV sizing for prediction of sPAR (< 13%), as well as STS predicted risk of mortality and access route (as a 3-grouped categorical variable) that both trended to differ significantly between the control and the sPAR groups. The impact of calcium volume in the upper quartile and PAR > mild at discharge on all-cause mortality were evaluated using a Cox proportional hazards model adjusted for variables potentially influencing mortality (age, sex, STS predicted risk of mortality and AVA at discharge). Log-rank test was performed to compare survival distributions. A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata 12 (StataCorp LP, College Station,Texas).

3. Results

3.1. Study population
Of the 324 patients evaluated for study inclusion, 22 patients where excluded. The MDCT quality was inadequate for calcium quantification in 10 patients (1 of these patients would have meet the composite endpoint of sPAR). THV function/degree of PAR could not be accurately determined from the available TTE in 10 patients (none of these patients underwent postdilatation), and 2 patients died (1 from coronary obstruction during the procedure, and 1 from cardiogenic shock immediately post-procedural) before pre-discharge TTE was performed. Thus, the final study cohort comprised 302 patients. A total of 46 (15%) patients reached the composite endpoint sPAR. Baseline clinical, echocardiographic, and MDCT characteristics of the study population are presented in Tables 1 and 1S (supplementary data). Median age was 83 years, 50% were female, and median STS predicted risk of mortality was 5.5%. There were no significant differences between the control and sPAR groups in any of the baseline characteristics.

3.2. Procedural data, in-hospital complications and pre-discharge echocardiographic data
Procedural data and pre-discharge echocardiographic data are depicted in Table 2 while frequencies of in-

hospital complications are depicted 2S (supplementary data). Mean ± SD (range) nominal THV oversizing relative to MDCT annular area was 17 ± 14% (−23 to 44%). Postdilatation was performed in 7% (21/302) of the patients and PAR > mild at discharge was present in 10% (30/302) of the patients. Mean THV oversizing was lower in the sPAR group compared to the control group, 13 ± 13% vs. 18 ± 14%, p=0.04. In the sPAR group, 57% had moderate PAR and 9% severe PAR at discharge. In 5 of 21 (24%) patients, postdilatation did not reduce PAR to≤mild at the predischarge echocardiography. In 2 of these patients the THV implanted was undersized relative to the annulus area, whereas the other 3 patients had upper LVOT calcium volumes in the upper quartile. Median upper LVOT calcium volume was 36 (11–82) mm3 in the 5 patients where postdilatation did not reduce PAR to≤mild vs. 13 (0–73) mm3 in the 16 patients where PAR was reduced to≤mild. Pre-discharge AVA was higher in the control group as compared to the sPAR group (Table 2).

3.3. Calcium analysis
Individual patient calcium volumes in relation to the anatomic region are shown in Fig. 2, and summarized in Table 3. There were no differences in the median contrast attenuation or the median calcium detection threshold between groups. sPAR patients had significantly more upper LVOT and overall LVOT calcium compared to patients in the control group. In contrast, aortic valve region calcium volume did not differ between groups. In ROC analysis, upper LVOT calcium volume had significantly higher discriminatory value regarding sPAR as compared to the overall LVOT calcium volume (Table 4). Aortic valve region calcium volume did not predict sPAR. If patients who underwent postdilatation were excluded from the analysis, the results were similar (Table 4S). THV oversizing predicted sPAR, AUC (95%CI) 0.75 (0.63–0.84), with an optimal cut-off point at 13%. In 22 sPAR patients with THV oversizing ≥ 13%, median (IQR) upper LVOT calcium volume was higher than in 24 sPAR patients less than 13% THV oversizing, 63 (30–75) vs. 0 (0–11) mm3; p < 0.0001. Overall, upper LVOT calcium volume was significantly more predictive of sPAR in 205 patients with THV oversizing ≥ 13% compared to 97 patients with THV oversizing<13%, AUC (95% CI): 0.83 (0.72–0.93) vs. 0.67 (0.51–0.74); p < 0.0001. Excluding 3 patients with THV undersizing from the 97 patients with THV oversizing<13% did not affect the predictive value of upper LVOT calcium volume for sPAR, AUC (95% CI): 0.67 (0.51–0.74) vs. 0.69 (0.53–0.77). The degree of annular calcium nodule protusion into the lumen predicted sPAR, AUC (95%): 0.72 (0.60–0.80). Of the 95 (31%) patients with calcium in the upper LVOT, 22 had one or more calcium nodules protruding ≥ 25% into the lumen. The combined endpoint of sPAR occurred in 19 of these 22 (86%) patients.

3.4. Multivariable analysis of predictors of sPAR
Results of multivariable logistic regression analysis for prediction of sPAR are shown in Table 5. Upper LVOT calcium volume ≥ 21mm3 and annular calcium protrusion ≥ 25%, but not overall LVOT ≥30mm3 calcium, independently predicted sPAR when adjusting for THV oversizing<13%, STS predicted risk of mortality, and access route.

3.5. Impact of calcium volume and PAR > mild at discharge on mortality Median (IQR) follow-up time with regard to survival status after TAVR was 1.4 (1.0–2.0) years ranging from 3 days to 3.8 years. During follow-up, 59 (20%) patients died. When adjusted for age, sex, STS predicted risk of mortality and AVA at discharge, neither upper LVOT calcium volume (HRadjusted, 0.8 (95% CI, 0.3–2.1); p=0.53) nor total aortic root calcium volume (HRadjusted, 1.2 (95% CI, 0.6–2.3); p=0.32) in the upper quartile was associated with mortality. PAR > mild was associated with increased all-cause mortality during the follow-up period, HRadjusted: 2.2 (95% CI, 1.2–4.7), p=0.02 (Fig. 3). Twelve-month mortality in the 5 patients in whom postdilatation did not reduce PAR to≤mild was 40% vs. 13% in the 16 patients with PAR reduced to≤mild.

4. Discussion

This study demonstrates an association between aortic root calcium and the risk of significant PAR (ie. PAR > mild and/or the need of postdilatation) in TAVR. Specifically, the calcium volume in the upper LVOT predicts sPAR better than overall LVOT calcification, while aortic valve region calcium does not influence the risk of sPAR. PAR > mild at discharge, but not the calcium volume per se, were associated with increased all-cause mortality in our cohort. In line with data from Khalique et al.8 our study shows that upper LVOT calcium, but not overall LVOT calcium, predicts sPAR independent of THV sizing. However, upper

LVOT calcium volume was significantly more predictive of sPAR in patients with THV oversizing ≥ 13% (the optimal cut off point for prediction of sPAR by THV sizing) compared to patients with THV oversizing<13%. The inverse relation between THV oversizing and PAR is well established, and generally 5–20% oversizing of the Sapien XT THV has been advised (taking into account the limited THV sizes available).[1,4,6,20] Thus our results probably reflects the fact that in patients with THV oversizing<13%, the presence of PAR to a greater extent was explained by inadequate oversizing rather that upper LVOT calcium. Importantly, this may have been a conscious choice as a larger valve size may have resulted in more severe annular oversizing which, in the setting of nodular calcification, may be associated with aortic root injury.[2,3] As THV size selection continues to improve through growing use of 3-dimensional imaging modalities and specific THV sizing guidelines, the contribution of inappropriate sizing to PAR most likely will decline.[4,6,20,26] Therefore, to continuously reduce the incidence of PAR, appropriate consideration of other contributing factors, such as calcium volume and distribution, remains crucial. Prospectively evaluated guidelines for sizing of the Edwards Sapien XT recommend a lower range of oversizing in the event of more than minimal LVOT calcification.[6] Further larger prospective studies are warranted to validate our results and to further specify the optimal degree of THV sizing in relation to calcium volume and distribution to balance the risk of PAR and aortic root injury. Data from randomized trials and registries show that PAR > mild is associated with a worse clinical outcome, including mortality.[1] Even mild PAR has been reported to be a predictor of mortality, albeit data are conflicting and therefore PAR > mild was chosen as endpoint in the present study.[27] Studies addressing the impact of calcium distribution on the risk of PAR have been limited in their ability to study clinical outcomes, largely due to limited cohort sizes. In contrast, our study confirmed the clinical significance of more than mild PAR at discharge with a 2-fold increase in 12-month all-cause mortality. In previous studies on aortic root calcification and pre-TAVR MDCT, there was large variation in the applied methodologies, thus direct comparisons between studies are not possible.[7–16] The varied methodology reflects the fact that aortic root and LVOT calcium assessment on contrast-enhanced pre-TAVR MDCT scans is challenging. Firstly, the complex anatomic nature of the aortic root makes it challenging to accurately perform 3-dimensional regional calcium quantification in a consistent fashion. In addition, contrast enhancement is essential in order to obtain detailed anatomical information regarding the aortic root and annulus. Consequently, using a threshold-based calcium quantification strategy is problematic since a fixed calcium detection threshold does not take into account the variability in contrast attenuation caused by issues related to e.g. acquisition- and patient characteristics. Most previous studies have applied various empiric fixed calcium-detection thresholds ranging from 500 to 850HU.[10–12] When applying a specific calcium quantification methodology across different scanners/acquisition protocols, a patient-specific calcium detection threshold adjusting for variation in contrast attenuation may be more appropriate. Recent data from Jilaihawi et al.[9] emphasize that the ability of aortic root calcium to predict PAR is dependent on the calcium detection threshold used, however even in that study a fixed threshold was used with no adjustment for the variation in contrast attenuation between individual MDCT scans. In order to comply with these issues, the present study used dedicated software that ensures perpendicular views along a centerline and provides 3-dimensional VOI definition capabilities allowing for granular regional calcium quantification in the aortic root and LVOT. Moreover, the present study incorporates patient-specific calcium detection thresholds to adjust for variability of mean contrast attenuation in the aortic lumen. The AUC value of 0.80 for discrimination of sPAR by upper LVOT calcium volume as found in the present study is in the upper range of AUC-values for calcium measures reported in other studies using different methodologies. [7–10,13,16] Our multicenter design with inclusion of MDCT examinations acquired with three different scanners and protocols increases the external validity of our calcium quantification method and our findings in general potentially making them more applicable to real-world clinical practice across different scanners and acquisition protocols. Finally, as opposed to previous studies, we evaluated the significance of protrusion of calcium nodules into the lumen at the annular level. Calcium nodular protrusion did significantly predict sPAR and there was a high rate (86%) of sPAR in patients with annular calcium nodule protrusion ≥ 25%. Although not as predictive as upper LVOT calcium volume, this simple metric is readily available during standard pre-TAVR MDCT planning. Reduction of PAR severity by procedural postdilatation has been proven feasible, however the use of postdilatation varies significantly between institutions.[28–30] We reported use of postdilatation in 7% of patients, which is in the lower range of what has been reported in previous studies. This may partly be explained by increased operator experience and more appropriate THV sizing through the use 3-dimensional imaging compared to studies performed earlier in the TAVR era.[29,30] Similar to a recent study

by Watanabe et al.,[28] we found that in approximately 24% of cases where postdilatation was performed, it did not reduce PAR to≤mild. The sample size in the current study does not allow for identification of specific predictors of non-response to postdilatation, but contributing factors may include high levels of calcium, malpositioning or excessive THV undersizing.[30] Of note, postdilatation is not without risks and has been reported to constitute an elevated risk for aortic root injury and possibly stroke.[3,29,30] The higher incidence of THV embolization in the sPAR group in this study was likely due to a combination of the use of postdilatation, lower degree of oversizing and higher prevalence of heavy, bulky calcifications potentially increasing the risk of THV displacement during balloon inflation.[31] Consequently, when considering whether or not to perform postdilatation during the procedure detailed information as provided by pre-TAVR MDCT may be of significant value. This study concerns the Edwards Sapien XT THV, but recently the newer generation Edwards Sapien 3 has emerged. The Sapien 3 valve, through the introduction of a sealing cuff and facilitated accurate positioning, has demonstrated lower rates of moderate/severe PAR compared to previous generations.[32] However, the incidence moderate/severe PAR is still around 3.5%, and with the well-established impact of PAR on mortality and the introduction of TAVR in younger and lower risk patients, uncovering factors associated with PAR remains important. [33,34] While the threshold of oversizing may be different with the Sapien 3 THV, there are no engineering explanations as to why calcium would not have similar relative impact on the risk of PAR.

5. Limitations

This study has the inherent limitations of an observational design. Furthermore, postdilatation was performed at the discretion of the treating operator based on intra-procedural TEE and/or angiography. Hence, there is no data confirming the actual severity of PAR before postdilatation. Grading of PAR can be challenging. However, all TTEs were analyzed by echo-cardiographers experienced in post-TAVR imaging and graded according to the VARC-2 criteria.[24] TEE may allow more accurate evaluation of PAR, but in the vast majority of centers, standard clinical post-TAVR follow-up imaging consists of TTE and therefore this modality was used in the current study. Importantly, patients were excluded if TTE quality did allow assessment of PAR severity. Several factors that were not assessed in the present study, including implantation depth, co-axiality relative to the orientation of the aortic root/LVOT and THV device type may play a role in causing PAR.

6. Conclusion

Upper, in contrast to overall, LVOT calcium, independently predicts PAR > mild and need for postdilatation. Moreover, upper LVOT calcium is more predictive of PAR > mild and the need for postdilatation in more oversized than less oversized THVs. Importantly, aortic valve region calcium does not appear to play any role in predicting PAR > mild and the need for postdilatation. Future prospective studies are warranted to elucidate whether THV size selection can be refined by quantitative assessment of calcium distribution in order to reduce PAR.

References

1. Genereux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? A comprehensive review of the literature. J Am Coll Cardiol. 2013;61:1125–1136.
2. Barbanti M, Yang TH, Rodes Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation. 2013;128:244–253.
3. Hansson NC, Norgaard BL, Barbanti M, et al. The impact of calcium volume and distribution in aortic root injury related to balloon-expandable transcatheter aortic valve replacement. J Cardiovasc Comput Tomogr. 2015;9:382–392.
4. Hansson NC, Thuesen L, Hjortdal VE, et al. Three-dimensional multidetector computed tomography versus conventional 2-dimensional transesophageal echocardiography for annular sizing in transcatheter aortic valve replacement: influence on postprocedural paravalvular aortic regurgitation. Cathet Cardiovasc Interv. 2013;82:977–986.
5. Blanke P, Schoepf UJ, Leipsic JA. CT in transcatheter aortic valve replacement. Radiology. 2013;269:650–669.
6. Binder RK, Webb JG, Willson AB, et al. The impact of integration of a multidetector computed tomography annulus area sizing algorithm on outcomes of transcatheter aortic valve replacement: a prospective, multicenter, controlled trial. J Am Coll Cardiol. 2013;62:431–438.
7. Feuchtner G, Plank F, Bartel T, et al. Prediction of paravalvular regurgitation after transcatheter aortic valve implantation by computed tomography: value of aortic valve and annular calcification. Ann Thorac Surg. 2013;96:1574–1580.
8. Khalique OK, Hahn RT, Gada H, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2014;7:885–894.
9. Jilaihawi H, Makkar RR, Kashif M, et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging. 2014;15:1324–1332.
10. Azzalini L, Ghoshhajra BB, Elmariah S, et al. The aortic valve calcium nodule score (AVCNS) independently predicts paravalvular regurgitation after transcatheter aortic valve replacement (TAVR). J Cardiovasc Comput Tomogr. 2014;8:131–140.
11. Marwan M, Achenbach S, Ensminger SM, et al. CT predictors of post-procedural aortic regurgitation in patients referred for transcatheter aortic valve implantation: an analysis of 105 patients. Int J Cardiovasc Imag. 2013;29:1191–1198.
12. Koos R, Mahnken AH, Dohmen G, et al. Association of aortic valve calcification severity with the degree of aortic regurgitation after transcatheter aortic valve implantation. Int J Cardiol. 2011;150:142–145.
13. Ewe SH, Ng AC, Schuijf JD, et al. Location and severity of aortic valve calcium and implications for aortic regurgitation after transcatheter aortic valve implantation. Am J Cardiol. 2011;108:1470–1477.
14. Leber AW, Kasel M, Ischinger T, et al. Aortic valve calcium score as a predictor for outcome after TAVI using the CoreValve revalving system. Int J Cardiol. 2013;166:652–657.
15. Schultz C, Rossi A, van Mieghem N, et al. Aortic annulus dimensions and leaflet calcification from contrast MSCT predict the need for balloon post-dilatation after TAVI with the Medtronic CoreValve prosthesis. EuroIntervention. 2011;7:564–572.
16. Watanabe Y, Lefevre T, Arai T, et al. Can we predict postprocedural paravalvular leak after Edwards SAPIEN transcatheter aortic valve implantation? Cathet Cardiovasc Interv. 2015;86:144–151.
17. Bapat V, Attia R. Transaortic transcatheter aortic valve implantation: step-by-step guide. Semin Thorac Cardiovasc Surg. 2012;24:206–211.
18. Willson A, Toggweiler S, Webb JG. Transfemoral aortic valve replacement with the SAPIEN XT valve: step-by-step. Semin Thorac Cardiovasc Surg. 2011;23:51–54.
19. Walther T, Mollmann H, van Linden A, Kempfert J. Transcatheter aortic valve implantation transapical: step by step. Semin Thorac Cardiovasc Surg. 2011;23:55–61.
20. Willson AB, Webb JG, Freeman M, et al. Computed tomography-based sizing recommendations for transcatheter aortic valve replacement with balloon-expandable valves: comparison with transesophageal echocardiography and rationale for implementation in a prospective trial. J Cardiovasc Comput Tomogr. 2012;6:406–414.
21. Barbanti M, Leipsic J, Binder R, et al. Underexpansion and ad hoc post-dilation in selected patients

undergoing balloon-expandable transcatheter aortic valve replacement. J Am Coll Cardiol. 2014;63:976–981.

22. Willson AB, Webb JG, Gurvitch R, et al. Structural integrity of balloon-expandable stents after transcatheter aortic valve replacement: assessment by multidetector computed tomography. J Am Coll Cardiol Intv. 2012;5:525–532.

23. Binder RK, Webb JG, Toggweiler S, et al. Impact of post-implant SAPIEN XT geometry and position on conduction disturbances, hemodynamic performance, and paravalvular regurgitation. J Am Coll Cardiol Intv. 2013;6:462–468.

24. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol. 2012;60:1438–1454.

25. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837–845.

26. Willson AB, Webb JG, LaBounty TM, et al. 3-dimensional aortic annular assessment by multidetector computed tomography predicts moderate or severe paravalvular regurgitation after transcatheter aortic valve replacement: a multicenter retrospective analysis. J Am Coll Cardiol. 2012;59:1287–1294.

27. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J. 2015;36:449–456.

28. Watanabe Y, Hayashida K, Lefevre T, et al. Is postdilatation useful after implantation of the Edwards valve? Cathet Cardiovasc Interv. 2015;85:667–676. 29. Daneault B, Koss E, Hahn RT, et al. Efficacy and safety of postdilatation to reduce paravalvular regurgitation during balloon-expandable transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2013;6:85–91.

30. Nombela-Franco L, Rodes-Cabau J, DeLarochelliere R, et al. Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. JACC Cardiovasc Interv. 2012;5:499–512.

31. Makkar RR, Jilaihawi H, Chakravarty T, et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple valve implants in the U.S. PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). J Am Coll Cardiol. 2013;62:418–430.

32. Yang TH, Webb JG, Blanke P, et al. Incidence and severity of paravalvular aortic regurgitation with multidetector computed tomography nominal area oversizing or undersizing after transcatheter heart valve replacement with the Sapien 3: a comparison with the Sapien XT. JACC Cardiovasc Interv. 2015;8:462–471.

33. Blanke P, Pibarot P, Hahn R, et al. Computed tomography-based oversizing degrees and incidence of paravalvular regurgitation of a new generation transcatheter heart valve. JACC Cardiovasc Interv. 2017;10:810–820.

34. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J. 2016;37:2252–2262.