Echocardiographic and angiographic assessment of paravalvular regurgitation after TAVI: optimizing inter-technique reproducibility

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Aims
Aortic regurgitation (AR) after transcatheter aortic valve implantation (TAVI) is often first diagnosed by angiography and then confirmed and followed-up by transthoracic echocardiography (TTE). Consistency between both methods is important for follow-up. We sought to determine inter-technique reproducibility of the assessment of paravalvular AR after TAVI.

Methods and results
The study included 165 patients treated with a self-expanding bioprosthesis and had angiography and TTE performed at a median interval of 4 days. TTE parameters of AR severity included VARC score (the average AR grade determined by the echocardiographic VARC-II criteria), pressure half time (PHT), regurgitation jet features in long-axis views (LAX score) and colour Doppler (CD) score (= paravalvular AR jet circumferential extent (%) + LAX score). Using receiver-operating characteristics curves, the cut-points that best defined an angiographic > mild AR were identified.

On TTE, AR was paravalvular in all cases, multi-jet in 28%, and predominantly (64%) detected in the commissural region between the right and left coronary sinuses. Using VARC-II criteria (combining at least two), TTE agreed with angiographic classification in 53% of cases (κ = 0.14). Greater than mild AR could better be defined by one of the following combinations of criteria: (i) LAX score > 4.25 and VARC-II score > 1.33; (ii) CD score > 11.5 and PHT < 400 ms. The combination of the CD score with PHT gave the best sum of sensitivity, specificity, positive, and negative predictive values.

Conclusions
Agreement between angiography and TTE (using the VARC-II criteria) in the grading of post-TAVI AR is modest, and this might have contributed to the inconsistency of data on the rate and fate of paravalvular AR. Inter-technique reproducibility can be improved using a combination of CD and hemodynamic parameters.

Keywords
Aortic regurgitation • Angiography • Doppler echocardiography • Transcatheter aortic valve implantation

Introduction
Transcatheter aortic valve implantation (TAVI) irreversibly changed the profile of the valve disease therapeutic armamentarium. Post-TAVI aortic regurgitation (AR), often paravalvular, is common and was shown to adversely affect morbidity, mortality, and reverse cardiac remodeling after TAVI.

There are important inconsistencies of data on the rate and fate of post-TAVI AR and its relation to patients’ outcomes. Intra-technique (transthoracic echocardiography-TTE) reproducibility is suboptimal and is thought to have contributed to those inconsistencies. Inter-technique reproducibility is another source of discrepancies unless systematically optimized.

Aortic root angiography, typically using Seller’s visual grading, is the first screening tool used in most laboratories for detection of post-implantation AR and guidance of timely corrective measures (e.g. post-dilation, valve-in-valve and, most recently, retrieval and reposition of the valve). A widespread trend is to perform TAVI without general anaesthesia making it as quick and simple as typical cardiovascular interventions. Angiography might, thus, become...
the only intraprocedural technique to detect AR or be combined with TTE under conscious sedation. Angiography is, however, inappropriate for longer-term follow up where TTE is the standard imaging method. Therefore, post-TAVI AR is often first diagnosed by angiography and then confirmed and followed-up by TTE. Both methods should provide an acceptable degree of consistency.

In the present study, we sought to investigate the consistency between echocardiographic and angiographic assessment of post-TAVI AR.

Methods

The study included patients with symptomatic severe aortic stenosis, who underwent TAVI based on the decision of a multidisciplinary team after providing written informed consent. Two hundred and five consecutive patients were initially included in the present study. Out of those patients, 12 were excluded due to the final angiographic acquisition performed while a catheter or a guide-wire was left passing through the implanted valve. Further 28 patients were excluded due to incomplete TTE data, defined as < two reliably analysable parameters of AR severity. In those patients, AR severity was defined, with modest confidence, as moderate in one patient, as mild in nine patients and as none-trace in the remainder based on colour Doppler (CD) data (n = 13), quantitative Doppler data (n = 9), continuous wave Doppler data (n = 5) or descending aortic flow profile (n = 1). Final analysis included 165 patients who were alive until hospital discharge and had both angiography and TTE performed at a median interval of 4 days (range: 2–7 days). Prosthesis sizing was based on the multislice computed tomography (MSCT)-based annular sizing in all cases. The cover index was calculated as: 100 × \( \frac{\text{prosthesis area}}{\text{MSCT annular area}} \) / prosthesis area.\(^{13}\)

Angiography

Aortography was performed at least 10 min after final valve implantation (or after post-dilation, if applicable) thus allowing for any spontaneous regression of paravalvular AR to occur prior to final assessment.\(^{14}\) The pigtail catheter was positioned in the upper third part of the frame of the self-expanding valve and at least 20 mL of contrast were injected at a rate of 20 mL/s into the aortic root. A single experienced investigator blinded to echocardiographic data (HT) visually graded the severity of AR according to the Sellers’ method.\(^{7}\) The same observer reanalysed 20 randomly selected angiograms at a median interval of 60 days. Intra-observer reclassification occurred in four cases (20%) with no > one class reclassification (kappa coefficient = 0.62, indicating a good agreement).\(^{15,16}\) Sellers’ grade I was defined as mild AR and Sellers’ grade ≥ II was defined as > mild AR.

Echocardiography

Echocardiographic analysis was performed by two cardiologists (OS and MA) blinded to angiographic data. The following parameters were measured according to the recommendations of the American Society of Echocardiography,\(^{17–20}\) European Association of Cardiovascular Imaging\(^ {17,18–20}\) : paravalvular AR jet circumferential extent (CE), AR jet pressure half time (PHT), duration and end-diastolic velocity of aortic diastolic flow reversal (DFR), regurgitation volume and fraction (RV/RF), and effective regurgitant orifice area (EROA). RV was calculated as the difference between the stroke volumes at the left and right ventricular outflow tracts using pulsed-wave Doppler. RF was calculated as the RV divided by the LVOI stroke volume.

CE from the CD parasternal short axis (PSAX) view was measured in the frame that shows high velocity mosaic colour that is continuous and not significantly different from preceding and following frames measuring the angle that contains the jet as an absolute value (degrees) and as a fraction (percentage) of the 360° face-of-a clock (Figure 1). Caution has been exercised to include the sum of the separate jets, not the paravalvular arc which includes the non-regurgitant spaces between jets.\(^{21}\)

Grading of AR severity

VARC-II criteria

Categorical grading of AR severity was based on integrating available valve academic research consortium (VARC-II) criteria,\(^{22}\) namely: CE, DFR, RV/RF, and EROA (Table 1). AR grade was based on the class agreed by all/the majority of available criteria. In case of discrepancy of available criteria, CE was always heavily weighted unless negative (due to a relatively high rate of false negative results of this parameter).

A continuous metric was generated to represent the average rank (0 = none-trace, 1 = mild, 2 = more than mild) of all available AR severity criteria assuming an equal weight of all criteria (VARC score). If all four criteria are measurable, a maximum total score of eight could be obtained.

CD-based AR grading

Four CD views were used to scan for AR; the PSAX view and three long-axis (LAX) views (parasternal LAX, apical 5-chamber and apical 3-chamber views). From the three LAX views, six different locations around the transcatheter valve can be identified (Figures 1 and 2).\(^{23}\)

LAX score

For each of the six LAX locations, a qualitative score was given for paravalvular AR jet features; 0 = no visible regurgitant flow, 1 = ill-defined turbulence within the stent that is not quantifiable, 2 = significant well-defined jet with the jet path visible from its origin until the valve stent inflow edge. This gives a theoretical range of 0–2/ LAX location and a theoretical range of 0 (no visible jets in any of the six locations) to 12 (significant jets seen in the six locations) for all locations combined (Figure 1).

CD score

CD data from LAX and PSAX views were combined to generate a CD score (= CE% + LAX score) (Figure 1). The maximum CD score possible is 112 although severe AR would typically have a score of ≥30–42.

Inter-observer variability of echocardiographic AR assessment

In randomly selected cases, echocardiographic analysis was performed by both observers (n = 30) and by the same observer (at a median interval of 49 days, n = 15) to test inter- and intra-observer reproducibility. Weighted kappa coefficient for AR grade (based on the VARC-II criteria) was 0.51 (consistent with a moderate
agreement\textsuperscript{15,16} for inter-observer comparison and 0.83 (consistent with an excellent agreement\textsuperscript{15,16}) for intra-observer comparison ($P$, 0.005 for both). The intraclass correlation coefficient for para-valvular AR jet CE was 0.91 (95% confidence limits, 0.82–0.96) for inter-observer comparison and 0.95 (95% confidence limits, 0.86–0.98) for intra-observer comparison ($P$, 0.001 for both).

**Statistical methods**

For numerical variables, visual inspection (of histograms) and Shapiro–Wilk test were used to determine normality of distribution. When nonparametric statistical methods were used, we summarized data as median and quartiles instead of means and standard deviations (SD). Categorical variables were summarized as frequencies and percentages.

Baseline patient characteristics were descriptively summarized. Differences between groups with different angiographic grades of AR were assessed by Kruskal–Wallis and Mann–Whitney U tests for continuous variables and by $\chi^2$ test for categorical variables. A kappa (k) statistic was used to determine the agreement on grading of AR severity between TTE and aortography. Receiver-operating characteristics (ROC) curves were generated for the diagnosis of $>$ mild AR by multiple quantitative echocardiographic parameters. The cut-points were defined using ROC curves on the basis of the highest sum of sensitivity and specificity for the definition of significant AR.

Statistical analysis was performed with SPSS 23 (IBM, Armonk, NY, USA). All probability values were two-tailed, and a value of $P$, 0.05 was considered significant.

**Results**

One hundred and sixty-five patients (age, 82 $\pm$ 5 years; 94 males) were included. All patients received a CoreValve bioprosthesis (Medtronic, Minneapolis, MN, USA), via a transfemoral ($n$ = 138), trans-subclavian or direct aortic access. The valve size was 29 mm in 45%, 31 mm in 32%, 26 mm in 20% and 23 mm in only 3% of patients, with an average cover index of 14.7 $\pm$ 4.9%. On post-implantation angiography, AR was graded as none-trace in 15 (9%), mild in 111 (67%), and $>=$mild in 39 (24%) patients. Postdilation was
performed in 21.7% and another valve (in-valve) was implanted in 5.2% of cases. Apart from male gender (76.3 vs. 52.4%, \(P = 0.007\)), there were no differences in baseline characteristics (Table 2) between those with and without mild AR.

**Echocardiographic assessment of AR**

**Number and location of AR jets**

On PSAX CD (n = 146), at least one paravalvular AR jet was seen in 101 patients (69%). A single jet was present in 73 (72%) and multiple jets in 28 (28%) patients (two jets in 24, three jets in 2 and four jets in 2 patients). Two-thirds (64%) of jets were detected in the sector of the 360° face-of-a clock that extends from 11’ to 3’ (Figure 2).

In those with PSAX showing no AR (45 cases), AR was revealed on LAX CD in 25 (false negative PSAX). Figure 2 shows the location of paravalvular AR jet(s) in PSAX and in LAX views. Jets originating at the non-coronary sinus region (posterior location in PLAX and apical 3-chamber views) were more likely to be missed in the PSAX view.

**AR grading according to the VARC-II criteria**

As shown in Table 3, although median values of the individual parameters (CE, RV, RF, and EROA) increased numerically with increasing angiographic severity of AR, there was a marked overlap (\(P > 0.05\) for RV, RF, and EROA).

CE% differed significantly (\(P = 0.008\)) between the classes (median[interquartile range-IQR]: 1[4], 7[10], and 9[8.5] % in none-to-trace,}

**Table 2 Baseline demographic, clinical and echocardiographic characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82.1 ± 5.2</td>
</tr>
<tr>
<td>Male</td>
<td>94 (57)</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>14.8 ± 9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.9 ± 5.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>55 (33)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>153 (93)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>58 (35)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>31 (19)</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>42 (25)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>22 (13)</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>71 (43)</td>
</tr>
<tr>
<td>III</td>
<td>89 (54)</td>
</tr>
<tr>
<td>IV</td>
<td>5 (3)</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.68 ± 0.16</td>
</tr>
<tr>
<td>AVA index (cm²/m²)</td>
<td>0.37 ± 0.11</td>
</tr>
<tr>
<td>Mean pressure gradient (mmHg)</td>
<td>48.7 ± 13.8</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.9 ± 10</td>
</tr>
<tr>
<td>Aortic annulus diameter (mm)</td>
<td>22.7 ± 2.8</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD or n (%).

AVA, aortic valve area; CABG, coronary artery bypass grafting; Logistic EuroSCORE, Logistic EuroSCORE predicted risk of mortality at 30 day; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.
mild, and >mild angiographic AR). When AR grading was based only on CE% (n = 121), grade agreement with angiography was achieved in 43% of cases (kappa statistic = 0.13) (Table 4A).

The average AR grade determined by the VARC II-parameters (VARC score), significantly differed between the AR angiographic grades (1[0.5] vs. 1.33[0.75] vs. 1.5[0.83], P = 0.03) but only when at least two criteria were combined (n = 101). Grade agreement with angiography was, however, achieved in only 53% of cases (kappa statistic = 0.14). Inter-technique agreement was lowest for none-trace (18%) AR (Table 4B). Extreme misclassification (i.e. from none-to-trace to >mild or vice versa) occurred only in two cases (2%).

AR grading using other criteria

PHT (n = 71) tended to be higher in patients with angiographic mild or less AR (450 [102] ms) than in those with >mild AR (398 [149] ms, P = 0.057). Based on the cut-point (500 ms) set per-guidelines\(^{18}\) for discriminating mild or less from >mild AR, agreement with angiographic grading was achieved in only 42% of cases (in 79% of cases with angiographic >mild and in only 23% of cases with mild or less AR). Using the ROC curve to better define a cut-point, 403 ms had the best sum of sensitivity (75%) and specificity (52%) to define >mild AR (area under the curve-AUC, 0.63) and improved agreement with angiography to 68%.

LAX CD view(s) were available in almost all cases (n = 164, 99%). LAX score showed a stepwise increase with increasing angiographic severity of AR (3[4] in none-trace, 4[4] in mild, and 6.5[2.8] in >mild AR, P < 0.001). CD score was available in 130 cases (79%) and increased significantly with increasing angiographic severity of AR (2[8.5] in none-trace, 11[14] in mild, and 18[10] in >mild AR, P < 0.001). Using ROC curves, the cut-points of the VARC score, LAX score, CD score, and PHT that best defined an angiographic >mild AR were identified (Table 5, Figure 3). Using those cut-points, the combination of LAX score and VARC score improved the specificity and the negative predictive value of identifying angiographic >mild AR to 78 and 87%, respectively (Figure 4A). The combination of the CD score with PHT gave the best sum of sensitivity (69%), specificity (91%), positive (85%), and negative (81%) predictive values (Figure 4B).

Discussion

The main findings of the present study are that (i) echocardiographic grading of post-TAVI AR (based on VARC II criteria) is frequently at odds with angiographic grading, especially when a single echocardiographic parameter is used, (ii) combining more...
echocardiographic criteria and adding LAX CD to the current VARC criteria improve inter-technique agreement, and (iii) greater than mild AR can be defined by one of the following combinations of criteria: (i) LAX score > 4.25 and VARC score (using at least two criteria) > 1.33; (ii) CD score > 11.5 and PHT < 400 ms.

Paravalvular AR is a frequent complication of TAVI that contributed to eroding its clinical benefit and limiting its extension into lower risk patients. Very important data on the natural history of post-TAVI AR are still, however, inconsistent. The reported rate of incidence ranged from 40 to 67% for trivial to mild and from 7 to 27% for moderate to severe AR.\(^1,2\) The fate of AR has been described as ‘improving’,\(^25\) ‘deteriorating’,\(^26\) ‘stable’,\(^27\) and ‘variable’\(^28\) in different reports. The reported association with clinical outcomes ranged from ‘no relation’\(^29\) to ‘a strong relation’ of even mild AR.\(^2\)

Many echocardiographic parameters used for quantitating native transvalvular AR are inherently unreliable in paravalvular leakage. This might, at least partially, explain the heterogeneity of data on post-TAVI AR and the discrepancy in AR grading between echocardiography and other methods (e.g. cardiac magnetic resonance-CMR).

While there was no difference between CMR and echocardiography in native AR\(^10,31\) or in post-surgical replacement AR\(^9,30\) quantification, important differences were reported in post-TAVI AR\(^9,30,32\). Kappa statistic of agreement between CMR and echocardiographic AR grading (based on the VARC-II criteria) was 0.33–0.36, consistent with a fair agreement.\(^5,16\) The rate of detection of > mild AR (as defined by CMR) by echocardiography (using VARC criteria, especially DFR and CE) was reported to be 19%.\(^5\)

Agreement between angiography and echocardiography has a special importance as they are the standard techniques for periprocedural and follow-up assessments, respectively. In a study by Sherif et al., angiographic and CMR grading of post-TAVI AR showed a substantial agreement (\(k = 0.72\)).\(^6\) Echocardiographic grading was, on the other hand, discordant with CMR (\(k = 0.20\)) and angiography (\(k = 0.14\)).\(^6\) Small sample size, relatively long interval between angiographic and echocardiographic studies (4 weeks) and using PLAX view as a sole echocardiographic view for AR assessment are, however, important limitations of that study. In another study by Mihara et al.,\(^24\) AR grading on CD transesophageal echocardiography was discordant with that determined by angiography in 44% of cases (kappa statistic = 0.20). In the present study, discordance between echocardiographic and angiographic grading of post-TAVI AR is further confirmed.

**CD criteria**

LAX CD (combining parasternal and apical views) was available in 99% of cases in the present study and was shown to be the most concordant echocardiographic parameter with angiography. LAX CD has been previously shown to better correlate with AR volume and fraction (as defined by CMR) than short axis CE.\(^21\)

Using angiography and LAX CD as a reference, we found a relatively high false negative rate (17%) of PSAX observations.
LAX views on the other hand, allow a nearly complete evaluation of the circumference of the stented valve. Complementing the PSAX CD with the more sensitive LAX views would reduce the rate of false negative observations and might explain the improved agreement with angiography when this parameter was added (to the VARC score or in the CD score).

The high false negative rate of the PSAX view is likely due to two factors; the level of the imaging plane being too aortic thus missing regurgitation at the lower edge of the valve stent, and the acoustic shadowing of the posterior paravalvular region by the stented valve apparatus and native valve calcification. The present study supports this latter theory since jets originating at the non-coronary sinus (posterior location in PLAX and apical 3-chamber views) were more likely to be missed in the PSAX view.

Even after consideration of the low sensitivity of PSAX view to detect jets at the non-coronary sinus, there seems to be a preferential vulnerability of the commissural region between the right and left coronary sinuses (RLC) to the development of paravalvular leaks after TAVI. In the present study, 64% of leaks were detected in only one-third of the 360° perspective that extends from 11' to 3' (mainly involving the right coronary sinus and the RLC) (Figure 2). This spatial distribution contrasts with the preferential development (≏70%33,34) of post-surgical paraprosthetic leaks at the commissural region between right and non-coronary sinuses opposite the membranous interventricular septum (from 8' to 11'). This finding may be due to the asymmetric calcification of the aortic valve with more heavily calcified non-coronary and right coronary cusps35 but possibly also to the deployment angle and depth of the self-expanding CoreValve.36,37

Although quantitative grading of AR is recommended by both echocardiographic guidelines and the VARC-II document, the present study showed a significant overlap in quantitative grading.

**Figure 4** Combining different echocardiographic parameters (A: long-axis score and VARC score; B: CD score and PHT) to define angiographic >mild AR.
when compared to angiographic grading. Rather than a pitfall of echocardiography, this finding may be due to the known inconsistent correlation of quantitative assessment of AR with angiographic classification and the significant overlap between angiographic grades.38,39

**Hemodynamic criteria**

Adding a hemodynamic index to the instantaneous CD parameters is an appealing approach. Invasively measured diastolic pressure gradient across the leaking bioprosthesis was shown to accurately represent the severity of AR and predict clinical outcomes.40,41 In the present study, PHT improved the agreement of echocardiography with angiography when added to a CD-based scheme. The proposed cut-point differentiating mild or less from >mild AR (400 ms instead of 500 ms) needs yet to be validated but reconciles with the hemodynamic context of post-TAVI AR. Small, stiff, and concentrically hypertrophied left ventricles with concomitant abnormal aortic compliance may lead to flow characteristics of the AR jet that are quite different from chronic AR.42

**Limitations**

Angiographic assessment of AR cannot distinguish central from paravalvular jet and provides a subjective qualitative grading that inconsistently correlates with quantitative assessment of AR.38,39 Those shortcomings limit its consideration as a ‘gold standard’, but rather emphasize the need for combination with echocardiography and the importance of inter-technique consistency. Alternative options are, nevertheless, limited. Cardiac magnetic resonance is a more precise and quantitative means of assessing chronic AR but correlates poorly with echocardiography in the post-TAVI setting.43 Furthermore, the inconsistency of definitions of AR severity44 and the inability to distinguish mild AR (common and likely harmful after TAVI) from normal flow44 are important limitations of AR assessment by CMR after TAVI.

The performance of aortography shortly after valve implantation might have limited the accuracy of AR assessment, because the nitrol film of the CoreValve may continue to expand after implantation. However, early post-implantation angiography is the routine method in the majority of laboratories and at least 10 min were mandatorily left before final aorticographic acquisition in the present study. When is the most appropriate time-point to assess AR after TAVI? This is a critical question given the conflicting data on the fate of PVLs, with the answer being yet awaited.

Angiographic and echocardiographic studies were performed sequentially (rather than simultaneously) under different hemodynamic circumstances. As Doppler data are impacted by the driving pressures, this might have introduced some variability to the results of both techniques.

In fact, all Doppler parameters, especially continuous-wave Doppler ones, are sensitive to LV filling characteristics which are subject to acute changes after TAVI. This could be, on one hand, considered a limitation of those parameters but can be, on the other hand, considered as an advantage. An index that accounts for the hemodynamics on either side of the aortic valve (e.g. LV compliance) should more accurately reflect not only the hemodynamic significance of an AR jet but also the underlying hemodynamic vulnerability. We think that one of the approaches to delineate the significance of mild PVLs (a matter of continuing debate) could be the use of those ‘hemodynamic’ parameters. All cases received a single device type (self-expanding), and generalization of the results to other devices should be cautious.

Finally, the studied group of patients is not a true consecutive series given the common existence of exclusion criteria (inadequate angiographic and/or echocardiographic studies). Adequacy of echocardiography demanded good-quality images of at least two of the parameters of AR severity (CD, quantitative Doppler, aortic flow criteria and/or PHT of AR jet). The rate of >mild AR in the present series is higher than usually reported for this type of transcatheter aortic valves, reflecting the selection bias by excluding cases with inadequate angiographic and/or echocardiographic study.

**Conclusion**

There is only a modest agreement between angiography and the individual echocardiographic parameters in the grading of AR severity after TAVI. This might account, at least partially, for the inconsistency of data on the incidence and fate of post-TAVI AR. Integrating multiple parameters (instead of relying on a single criterion) and adding more parameters (CD and hemodynamic) to the VARC-II criteria improve inter-technique reproducibility. Combination criteria for determining the severity of AR, such as those proposed in the present study, should be validated in terms of their association with clinical endpoints.

**Conflict of interest**: None declared.

**References**


