5-Year outcomes after transcatheter aortic valve implantation: Focus on paravalvular leakage assessed by echocardiography and hemodynamic parameters

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Abstract

Objectives: We sought to assess the impact of echocardiographic and hemodynamic grading of paravalvular leakage (PVL) after transcatheter aortic valve implantation (TAVI) on the prediction of 5-year mortality. PVL after TAVI is known to influence outcome after TAVI. Yet, present available data of long-term outcomes and especially the comparison of different modalities for measurement of PVL is little.

Methods: We performed a retrospective single-center cohort study and compared the prognostic value of echocardiographic PVL grading as well as the aortic regurgitation index (ARI) pre- and post-TAVI. Univariable and multivariable Cox proportional regression analysis generated hazard ratios for mortality.

Results: A total of 464 patients underwent TAVI at our center between August 2012 and December 2014, with self-expandable CoreValve (11%) or balloon-expandable Sapien XT (47.4%) and Sapien 3 (41.6%) valves. Overall 5-year mortality was 52.4% (243/464). Echocardiographic classes of PVL at discharge showed a significant \((p = 0.002)\) association with 5-year mortality, mild PVL remained as an independent predictor for 5-year mortality in multivariable analysis (hazard ratio: 1.642 [95% confidence interval: 1.235–2.182]; \(p = 0.001\)). Grades of PVL as assessed during the procedure by ARI (below the previously defined cut-off of 25) did not show a significant association with 5-year mortality \((p = 0.417\) and \(p = 0.995\), respectively).

Conclusions: Even mild PVL assessed by echocardiography was an independent predictor for 5-year survival, whereas hemodynamic measurements did not help to identify PVLs that are relevant to 5-year survival.

Keywords: aortic regurgitation index, ARI, paravalvular leakage, TAVI

Abbreviations: ARI, aortic regurgitation index; DBP, diastolic blood pressure; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEDP, left ventricular end-diastolic pressure; PVL, paravalvular leakage; SBP, systolic blood pressure; TAVI, transcatheter aortic valve implantation.

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1 | INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has become the standard therapy in the elderly patient with severe aortic stenosis at high surgical risk and is gaining importance also in patients with moderate surgical risk (1–3). Usually, transvalvular gradients are more favorable after TAVI compared with surgical bioprostheses, whereas the incidence of paravalvular leaks (PVLs) is lower with surgical valves.1,2 Moderate or severe PVLs after TAVI are associated with an increased risk of death and some but not all studies suggested that even mild PVLs were associated with impaired survival.3–7

PVL can be visualized by different modalities including echocardiography,8 angiography,9 cardiovascular magnetic resonance,10 or new techniques like video densitometry.11 It is known that PVL is strongly influenced by the loading conditions and therefore may vary between measurements. In addition, each of the imaging criteria for grading PVL has a subjective element. Therefore, a study by Sinning et al.12 demonstrating that hemodynamic assessment may improve the grading of PVL with respect to the prediction of survival was an important contribution to PVL assessment. For this purpose, they proposed the aortic regurgitation index (ARI) which is calculated as the ratio of the difference in aortic and left ventricular end-diastolic pressures (LVEDPs) and the aortic peak systolic pressure. Specifically, Sinning et al.13 showed that an ARI < 25 was highly predictive of survival in patients undergoing TAVI. They improved the ARI by establishing the ARI ratio, which is calculated as the ratio of ARI after the procedure to ARI before the procedure. Sinning et al.13 found that within the subset of ARI < 25 only an ARI ratio < 0.6 was associated with a relevant increase in 1-year-mortality after TAVI with self-expanding valves.13,14

Over the years the incidences of PVL after TAVI have substantially decreased due to improvements in valve design and operator experience.15,16 Short-term data have been presented for the different modalities of accessing PVL7,9,12 and hemodynamic measurements have been improved by adding preprocedural measurements13 but long-term data for even mild PVL is lacking. As our research group already presented a 1-year follow-up for PVL after TAVI,7 where mild PVL assessed by echocardiography was an independent predictor for 1-year survival, we analyzed the predictor of mild PVL in the cohort at our center in a 5-year-follow-up.

2 | MATERIALS AND METHODS

2.1 | Study population

In this retrospective single-center study (University Heart Center, Bad Krozingen, Germany), we included 464 patients who underwent TAVI from August 2012 to December 2014. Survival and clinical status was followed for 5 years in all patients. The study was approved by the Institutional Clinical Research and Ethics Committee (registration number 472/12) and all patients gave written informed consent.

2.2 | TAVI procedure

Each patient was discussed in the multidisciplinary heart team for eligibility, procedural feasibility, access route, valve type, and size.17 Patients were primarily assessed by transthoracic echocardiography, systolic annular dimensions were obtained by computed tomography angiography as a planimetric area measurement with subsequent calculation of an effective annulus diameter as previously described.8,19 The choice of prosthesis type was made by the heart team, taking into account the height of the coronary orifices, the extent, and distribution of calcium as well as annulus sizes. Patients underwent TAVI in general anesthesia through transfemoral approach, as described previously.20

2.3 | Hemodynamic assessment

After successful placement of the valve and postdilatation if needed, ARI was measured as previously described (12). The gradient between diastolic blood pressure (DBP) in the aorta and the LVEDP and the systolic blood pressure (SBP) were calculated over several heart cycles. The ARI was calculated according to the previously described formula ([DBP – LVEDP]/SBP) × 100). For dichotomization, we used the cut-off value of 25 that had been shown to be most closely related to survival in previous studies.5,12 Additionally, we compared the subsets defined by ARI < 25 plus ARI ratio (ARIoff/ARIpre) < 0.6, ARI < 25 plus ARI ratio ≥ 0.6 and ARI ≥ 25.13

2.4 | Assessment of PVL

Transthoracic echocardiographic examination was performed before discharge. Different echocardiographers not having attended the procedure assessed prosthesis function and evaluated PVL in accordance with the Valve Academic Research Consortium-2 criteria.21,22 In general, echocardiography was assessed by two independent echocardiographers and differences were settled by consensus. Categories used for describing echocardiographic PVL were non/trace, mild, moderate, and severe as semi-quantitative parameters.

2.5 | Follow-up

As part of our routine quality assurance program, patients with TAVI were monitored with contacts by questionnaire and standardized telephone calls at 30 days, 6 months, 1 year, and yearly thereafter. For patients reporting events or not responding, the referring cardiologists and/or general practitioners were contacted for further information. If needed, we obtained additional information on circumstances of death from relatives or caregivers.
2.6 Statistical analysis

Statistical analysis was performed by IBM SPSS version 26.0 statistical software. Continuous variables are presented as mean ± 5D and categorical variables as frequencies and percentages. Continuous variables were tested with Kolmogorov–Smirnov test for normal distribution. For nonnormally distributed continuous variables, we used Mann–Whitney-U test comparing two groups and the Kruskal–Wallis test for more than two groups. Testing of categorical variables was performed by χ² test.

Cumulative event rates were assessed according to the Kaplan–Meier method and compared by log-rank test. We derived

| TABLE 1 Clinical characteristics for survivors versus nonsurvivors in 5-year follow-up |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| All patients (n = 464) | Survivors (n = 221) | Nonsurvivors (n = 243) | p Value |
| Age (years) | 82.6 ± 5.8 | 81.8 ± 5.5 | 82.2 ± 6.1 | 0.011 |
| Female | 255 (55.0) | 125 (56.6) | 130 (53.5) | 0.508 |
| Logistic EuroSCORE (%) | 21.5 ± 16.8 | 16.8 ± 13.1 | 25.7 ± 18.5 | <0.001 |
| Height (cm) | 165.5 ± 8.8 | 165.3 ± 8.3 | 165.7 ± 9.8 | 0.750 |
| Weight (kg) | 73 ± 15.5 | 73.4 ± 14.4 | 72.6 ± 16.5 | 0.408 |
| Mean aortic gradient (mm Hg) | 45.5 ± 14.3 | 47.6 ± 13.7 | 43.7 ± 14.6 | 0.003 |
| LVEF (%) | 51.6 ± 12.5 | 52.5 ± 12.2 | 50.9 ± 12.8 | 0.117 |
| Arterial hypertension | 425 (91.6) | 204 (92.3) | 221 (90.9) | 0.598 |
| Dyslipidemia | 322 (69.4) | 160 (72.4) | 162 (66.7) | 0.181 |
| Diabetes | 126 (27.2) | 54 (24.4) | 72 (29.6) | 0.209 |
| Glomerular filtration rate | 48.2 ± 20.3 | 52.2 ± 19.1 | 44.6 ± 20.6 | <0.001 |
| Coronary artery disease | 313 (67.5) | 148 (67) | 165 (67.9) | 0.830 |
| Extracardiac arterial disease | 156 (33.6) | 61 (27.6) | 95 (39.1) | 0.009 |
| Cerebrovascular disease | 99 (21.3) | 48 (21.7) | 51 (21.0) | 0.848 |
| Pulmonary hypertension | 231 (49.8) | 87 (39.4) | 144 (59.3) | <0.001 |
| Previous myocardial infarction | 83 (17.9) | 34 (15.4) | 49 (20.2) | 0.180 |
| Previous CABG | 52 (11.2) | 21 (9.5) | 31 (12.8) | 0.267 |
| Previous aortic valve surgery | 13 (2.8) | 6 (2.7) | 7 (2.9) | 0.914 |
| Aortic regurgitation | 0.146 |
| None/trace | 100 (21.6) | 45 (20.4) | 55 (22.6) |
| Mild | 311 (67) | 144 (65.2) | 167 (68.7) |
| Moderate | 47 (10.1) | 27 (12.2) | 20 (8.2) |
| Severe | 6 (1.3) | 5 (2.3) | 1 (0.4) |
| Mitral regurgitation | 0.038 |
| None/trace | 35 (7.5) | 23 (10.4) | 12 (4.9) |
| Mild | 303 (65.3) | 147 (66.5) | 156 (64.2) |
| Moderate | 111 (23.9) | 43 (19.5) | 68 (28.2) |
| Severe | 15 (3.2) | 8 (3.6) | 7 (2.9) |

Note: Values are mean ± standard deviation or n (%).

Abbreviations: CABG, coronary artery bypass graft; EuroSCORE, European System for Cardiac Operative Risk Evaluation; LVEF, left ventricular ejection fraction.
hazard ratios (HRs) with associated 95% confidence intervals from Cox proportional hazards models. To adjust for differences in baseline and procedural variables between the strata defined by PVL and to identify independent predictors of mortality we fitted multivariable Cox models with variables from Tables 1 and 2 that showed a difference between survivors and nonsurvivors after 5-year follow-up at \( p < 0.1 \). Statistical significance was assumed when the null hypothesis could be rejected at \( p < 0.05 \).

3  RESULTS

3.1  Study population

Our retrospective single-center study comprised 464 consecutive patients. The baseline characteristics of these patients are shown in Table 1. Mean age was 82.6 years, 55.0% were female and the mean logistic EuroSCORE for Cardiac Operative Risk Evaluation (EuroSCORE) was 21.5 ± 16.8%. The vital status after 5 years could be assessed in all patients. A total of 243 (52.4%) patients died during the surveillance period. As shown in Table 1, patients who died were older, had a significantly higher logistic EuroSCORE, a higher mean aortic gradient, a lower glomerular filtration rate, a higher prevalence of pulmonary hypertension and extracardiac arterial disease, as compared with survivors. Procedural characteristics of the study group are shown in Table 2. Most used valve types were the balloon-expandable Sapien XT (N = 220) and Sapien 3 (N = 193), self-expandable CoreValve was implanted in 51 patients.

3.2  Assessment of PVL

ARI measurement at the time of intervention was available in 422 (90.9%) patients and calculation of the ARI ratio was available in 418 (90%) patients. 206 (48.8%) patients had with an ARI below the prespecified cut-off of 25, suggesting relevant PVL. PVL assessed by transthoracic echocardiography could be obtained in 455 (98%) patients before discharge. This revealed none/trace, mild and moderate PVL in 169 (37.1%), 267 (58.7%), and 19 (4.2%), respectively. There was no severe PVL. Table 3 indicates the distribution of PVL among the different valve types. The self-expandable CoreValve showed the lowest proportion of none/trace PVL (24%) compared to Sapien XT (36%) and Sapien 3 (41.9%). Only one patient (0.5%) had moderate PVL with a Sapien 3 valve, whereas we found moderate PVL in five patients (10%) with a CoreValve.

3.3  PVL and 5-year mortality

Overall median follow-up was 1402 days (interquartile range of 510–1825 days). Five-year mortality stratified by classes of PVL as assessed by echocardiography, ARI and ARI ratio is shown in Figures 1–3, respectively.

With echocardiographic assessment, we found a significant association between echocardiographic classes of PVL at discharge and 5-year mortality (Figure 2; \( p = 0.003 \)), both in the univariable \( (p = 0.002) \) and in the multivariable \( (p = 0.003) \) analysis. HRs (95% confidence interval) were 1.642 (1.235–2.182), \( p = 0.001 \), for mild and 1.828 (0.990–3.376), \( p = 0.054 \), for moderate PVL in the univariable analysis.

In the multivariable analysis that included all differences in survivors versus nonsurvivors with a significance level <0.1, adjusted HRs were 1.655 (1.240–2.209), \( p = 0.001 \), for mild and 1.568 (0.837–2.938), \( p = 0.160 \), for moderate PVL. Other independent predictors of 5-year mortality were logistic EuroScore, a higher gradient, a higher prevalence of pulmonary hypertension, and extracardiac arterial disease, as compared with survivors. Procedural characteristics of the study group are shown in Table 2. Most used valve types were the balloon-expandable Sapien XT (N = 220) and Sapien 3 (N = 193), self-expandable CoreValve was implanted in 51 patients.

| Note: Values are mean ± or n (%). |
| --- |

### TABLE 2 Procedural characteristics for survivors versus nonsurvivors in 5-year follow-up

| All patients (n = 464) | Survivors (n = 221) | Nonsurvivors (n = 243) | p Value |
| --- | --- | --- | --- |
| Valve | 0.029 |
| CoreValve | 51 (11) | 22 (10) | 29 (11.9) |
| Sapien XT | 220 (47.4) | 93 (42.1) | 127 (52.3) |
| Sapien 3 | 193 (41.6) | 106 (48) | 87 (35.8) |
| Valve size (mm) | 0.701 |
| 19 | 1 (0.5) | 1 (0.5) | -- |
| 23 | 132 (28.4) | 58 (26.2) | 74 (30.5) |
| 26 | 220 (47.4) | 109 (49.3) | 111 (45.7) |
| 29 | 102 (22) | 49 (22.2) | 53 (21.8) |
| 31 | 9 (1.9) | 4 (1.8) | 5 (2.1) |
| Predilatation | 246 (53) | 104 (47.1) | 142 (58.4) | 0.014 |
| Postdilatation | 50 (10.8) | 23 (10.4) | 27 (11.1) | 0.807 |
| New pacemaker | 133 (28.7) | 55 (24.9) | 78 (32.1) | 0.086 |

### TABLE 3 Distribution of echocardiographic PVL and valve type

| Grading of PVL | CoreValve (n = 50) | Sapien XT (n = 214) | Sapien 3 (n = 191) | p Value |
| --- | --- | --- | --- | --- |
| None/trace | 12 (24) | 77 (36) | 80 (41.9) |
| Mild | 33 (66) | 124 (57.9) | 110 (57.6) |
| Moderate | 5 (10) | 13 (6.1) | 1 (0.5) |

Note: Values are mean ± or n (%).

Abbreviation: PVL, paravalvular leakage.
With hemodynamic assessment. There was no association of 5-year mortality with the cut-off of ARI at 25 (Figure 3; \( p = 0.995 \)). HR of ARI \( \geq 25 \) in univariable analysis was 0.994 (0.762–1.296; \( p = 0.965 \)). Analysis of the ARI ratio by the predefined groups of ARI < 25 and ARI ratio < 0.6, ARI < 25, and ARI ratio \( \geq 0.6 \) or ARI \( \geq 25 \) found also no association of 5-year mortality (\( p = 0.306 \)).

**DISCUSSION**

As our main finding, we report that even mild PVL assessed by echocardiography was strongly associated with long-term survival after TAVI. We found a significant increase in 5-year mortality with even mild PVL by 1.6 fold as compared with no or trace PVL, and this
association prevailed after multivariate adjustment. Numerically, an even larger impact on mortality was found with moderate PVL on echocardiography at discharge. Yet, statistical significance was missed, which may be explained by low numbers. PVL assessed by transthoracic echocardiography is known to be independently associated with 1-year-mortality. However, the association of even mild PVL with mortality was shown by some but not all previous studies on TAVI.

Similar to our previous findings during short-term follow-up, ARI was not associated with 5-year mortality in a cohort of patients undergoing TAVI with both balloon- and self-expandable devices. In addition to our former analysis of the 1-year mortality, we calculated the ARI ratio and analyzed the impact of the previously defined groups (at ARI < 25 and ARI ratio < 0.6, ARI < 25, and ARI ratio ≥ 0.6 or ARI ≥ 25) on 5-year mortality. This refinement of the hemodynamic concept of ARI did not improve the prediction of 5-year mortality in our cohort. Our findings are at variance with the study of Sinning et al. that established the concept of ARI and other studies. There are differences to be highlighted between the previous study and the current: Contrary to our present study, the previous study of Sinning et al. exclusively used one type of self-expandable valve design and none of the patients underwent TAVI in general anesthesia. ARI and ARI ratio might still be a parameter for self-expandable valve types but does not seem to be suitable for the prediction of survival for all valve types. With contemporary valve designs and procedural measures to minimize PVLs, the rate of more than mild PVL was low in our cohort and self-expandable valve types were only a few, compared to studies, that showed an association on mortality.

In this analysis, we had only patients with general anesthesia, which may have affected the study results. Left ventricular loading conditions are modified by general anesthesia to a variable extent and might have influenced intraprocedural measurements. The investigators of Source 3 reported no significant differences between conscious sedation and general anesthesia in procedural and clinical outcomes. There were, however, slightly more moderate PVLs (2.2% vs. 0.8%; \( p = 0.044 \)) in patients with conscious sedation as compared with general anesthesia. This difference might have been caused by a less frequent use of transoesophageal echocardiography with conscious sedation. Long-term data for comparison of conscious sedation and general anesthesia is lacking and the rate of moderate PVL has to be taken into account if analyzing data on long-term survival in the future.

The distribution of PVL among different valve types (Table 3) indicates that valve design improvements substantially decreased moderate PVL in the modern Sapien 3. Nevertheless, valve type did not emerge as an independent risk factor for death in our multivariable analysis. We cannot exclude, however, that with a larger sample size the different distribution of PVL among valve types would have resulted in a significant association of valve type with mortality.

As we did not perform serial echocardiography, we cannot present data on how many PVL's resolved or developed, post-interventionally. Yet, it has been shown previously that during the early course after TAVI changes in PVL are negligible. Hence, PVL before discharge adequately reflects this, therefore, it is reasonable to assume that our findings also apply to PVL at the completion of the procedure. The impact of PVL on survival, thus, suggests that more than trace PVL should be corrected by more aggressive treatment such as additional balloon inflations.

**5 | LIMITATIONS**

Although we present a long-term follow-up, the number of patients in correlation to the incidence of more than mild PVL was low. The low variability in the extent of PVL across the study cohort may have
limited the power to detect a prognostic impact of ARI. Likewise, we were unable to apply the advanced echocardiographic classification of PVL, published after recruitment of this cohort.\textsuperscript{28} Assessment of PVL is very subjective, we did not assess inter- or intraobserver variability as we had more than 10 experienced echocardiographers during the observation period. Further modalities like video densitometry to quantify PVL were not used in this study.\textsuperscript{11}

As we report a long-term follow-up, modern valve types as used today in clinical routine could not be depicted in this study. ARI showed its effects mainly in self-expandable valves like CoreValve prostheses,\textsuperscript{12} which were implanted only in a minority of patients in our cohort. Yet, the contrary findings in the literature that hemodynamic measurements work better in self-expanding valves compared to balloon-expandable valves, cannot be clarified by this study as this issue might be influenced by hidden confounders.

In contrast to our previously reported 1-year follow-up, we here report only single-center findings at our center. Although we performed multivariable adjustments, we cannot exclude that some unknown confounders affected our study results.

6 | CONCLUSION

Echocardiographic assessment before discharge was superior to hemodynamic assessment to estimate the impact of PVL after TAVI on long-term survival. It outperformed intraprocedural hemodynamic assessment including ARI and ARI ratio. Minor degrees of PVL are independently associated with long-term mortality. Thus, efforts are still needed to minimize PVL by choosing optimized prosthesis designs and appropriate procedural measures.

6.1 | Impact on daily practice

PVL after TAVI should be avoided as much as possible as even minor degrees of PVL are independently associated with long-term mortality. Valve manufacturers should continue their efforts in the optimization of valve designs.

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CONFLICT OF INTERESTS

Franz-Josef Neumann reports that his institution has received research grants, consultancy fees, and speaker honoraria to form Daiichi Sankyo, Astra Zeneca, Sanofi-Aventis, Bayer, The Medicines Company, Bristol, Novartis, Roche, Boston Scientific, Biotronik, Medtronic, Edwards und Ferrer. The other authors declare that there are no conflict of interests.

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