JACC: CARDIOVASCULAR INTERVENTIONS VOL. 5, NO. 8, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2012.04.011

Impact of Paravalvular Leakage on Outcome in Patients After Transcatheter Aortic Valve Implantation

Mariuca Vasa-Nicotera, MD,* Jan-Malte Sinning, MD,* Derek Chin, MD,† Tiong Keng Lim, MD,† Tomasz Spyt, MD,† Hasan Jilaihawi, MD,† Eberhard Grube, MD,* Nikos Werner, MD,* Georg Nickenig, MD,* Jan Kovac, MD†

Bonn, Germany; and Leicester, United Kingdom

Objectives The aim of this study was to evaluate the performance of the aortic regurgitation (AR) index as a new hemodynamic parameter in an independent transcatheter aortic valve implantation (TAVI) cohort and validate its application.

Background Increasing evidence associates more-than-mild periprosthetic aortic regurgitation (periAR) with increased mortality and morbidity; therefore precise evaluation of periAR after TAVI is essential. The AR index has been proposed recently as a simple and reproducible indicator for the severity of periAR and predictor of associated mortality.

Methods The severity of periAR was evaluated by echocardiography, angiography, and periprocedural measurement of the dimensionless AR index = ([diastolic blood pressure − left ventricular end-diastolic pressure]/systolic blood pressure) × 100. A cutoff value of 25 was used to identify patients at risk.

Results One hundred twenty-two patients underwent TAVI by use of either the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) (79.5%) or the Edwards-SAPIEN bioprosthesis (Edwards Lifesciences, Irvine, California) (20.5%). The AR index decreased stepwise from 29.4 ± 6.3 in patients without periAR (n = 26) to 28.0 ± 8.5 with mild periAR (n = 76), 19.6 ± 7.6 with moderate periAR (n = 18), and 7.6 ± 2.6 with severe periAR (n = 2) ($p < 0.001$). Patients with AR index <25 had a significantly increased 1-year mortality rate compared with patients with AR index ≥25 (42.3% vs. 14.3%; $p < 0.001$). Even in patients with none/mild periAR, the 1-year mortality risk could be further stratified by an AR index <25 (31.3% vs. 14.3%; $p = 0.04$).

Conclusions The validity of the AR index could be confirmed in this independent TAVI cohort and provided prognostic information that was complementary to the severity of AR. (J Am Coll Cardiol Intv 2012;5:858–65) © 2012 by the American College of Cardiology Foundation

From the *Medizinische Klinik und Poliklinik II, Universitätsklinikum Bonn, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany; and the †Department of Cardiology, Glenfield University Hospital, Leicester, United Kingdom. Dr. Jilaihawi is a consultant for Edwards Lifesciences, St. Jude Medical, and Venus Medtech. Dr. Grube is proctor for CoreValve/Medtronic. Dr. Kovac is proctor for CoreValve/Medtronic and Edwards-SAPIEN. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Vasa-Nicotera and Sinning contributed equally to this work.

Manuscript received April 5, 2012, accepted April 12, 2012.

With more than 50,000 implantations worldwide, transcatheter aortic valve implantation (TAVI) has increasingly become an alternative treatment strategy for patients with severe aortic stenosis regarded at high risk or inoperable by open-heart surgery (1–10). However, significant concerns are raised around the higher, mostly procedure-related incidence of paravavular leakage. Because transcatheter heart valves are implanted in a sutureless fashion using oversizing to expand a stent at the level of the aortic annulus, several etiologies can be invoked to explain periprosthetic aortic regurgitation (periAR) after TAVI, such as heavily calcified cusps, suboptimal placement of the prosthesis, and/or annulus-prosthesis-size mismatch. Recently published studies report an incidence of periAR in more than 70% of all TAVI patients that are graded as moderate/severe in approximately 10% to 28% of the patients (1,2,4,5,8–17).

Because evidence is growing that more-than-mild periAR after TAVI is associated with dramatically increased mortality and morbidity, precise evaluation of aortic regurgitation (AR) during the procedure is essential to take effective countermeasures but remains challenging, despite the recently published Valve Academic Research Consortium (VARC) criteria (18–23). Recently, the AR index as an objective hemodynamic parameter has been introduced for the precise assessment of the severity of periAR during the TAVI procedure to take effective countermeasures, such as post-dilation, snaring, or valve-in-valve implantation to decrease periAR if necessary (9).

The objective of this study was to evaluate the impact of moderate/severe periAR and to validate the AR index on outcome in an independent TAVI cohort.

Methods

Patient cohort. Between January 2007 and March 2011, 122 patients with severe aortic stenosis regarded at high risk or inoperable by open-heart surgery underwent TAVI at Glenfield University Hospital in Leicester, United Kingdom. Transcatheter aortic valve implantation patients were included in this prospective study, which complies with the Declaration of Helsinki and was approved by a locally appointed ethics committee, after written informed consent was obtained. Acceptance for TAVI required consensus by the multidisciplinary Heart Team. Patient screening, selection, and device implantation has been described previously (24).

The TAVI was performed with the 3rd Generation 18-F CoreValve prosthesis (CoreValve Revalving Technology, Medtronic, Minneapolis, Minnesota) or the Edwards-SAPIEN valve prosthesis (Edwards Lifesciences, Irvine, California). Annulus dimension was evaluated by transesophageal echocardiography (TEE) and angiography. All TAVI procedures were performed under general anesthesia and echocardiographic control by TEE. After TAVI, severity of periAR was assessed angiographically, echocardiographically by TEE, and hemodynamically. Patients were followed up in the outpatient clinic of the hospital. The primary endpoint of this study was all-cause mortality at 1 year. Secondary endpoint was the occurrence of moderate/severe periAR defined according to the definition of the VARC (18). Information about the cause of death was obtained from the treating hospital or general practitioner.

Assessment of periAR. The occurrence and degree of periAR was evaluated by angiography immediately after valve deployment and by intraprocedural TEE/TTE with an established integrative approach for semi-quantitative grading according to the recently published VARC criteria (18,19).

Simultaneous pressure measurements in the left ventricle and in the ascending aorta were performed with fluid-filled catheters before and after the procedure, in all patients. All hemodynamic measurements were averaged over 3 cardiac cycles. The dimensionless AR index was calculated retrospectively by an independent cardiologist who was unaware of the degree of periAR and the clinical outcome, according to the following formula (9): ([diastolic blood pressure (DBP) − left ventricular end-diastolic pressure (LVEDP)]/systolic blood pressure) × 100.

Measurement of the prosthesis implantation depth. The implantation depth of the prosthesis in the left ventricular outflow tract was measured with the final angiogram of the aorta with consistent C-arm angulation (perpendicular alignment of all 3 aortic cusps visible in the same plane before the TAVI procedure). The depth of implantation was defined as the distance from the native aortic annular margin on the side of the non- and left-coronary cusp, respectively, to the most proximal edge of the deployed stent-frame on the corresponding side.

Statistical analysis. Statistical analyses were conducted with IBM SPSS Statistics (version 20.0.0, IBM Corporation, Somers, New York). Data are presented as mean ± SD if normally distributed or as median and interquartile range if not normally distributed. Categorical variables are given as frequencies and percentages. Continuous variables were tested for differences with the Student *t* test or the analysis of variance test, when comparing more than 2 groups. For categorical variables, the chi-square test was used for further analysis. Pearson's correlation coefficient was used to establish associations.

Abbreviations and Acronyms

AR = aortic regurgitation
DBP = diastolic blood pressure
EuroSCORE = European system for cardiac operative risk evaluation
LVEDP = left ventricular end-diastolic pressure
periAR = periprosthetic aortic regurgitation
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography
VARC = Valve Academic Research Consortium

In the development cohort from Bonn, receiver operating characteristic curve analysis was used to determine the cutoff value for the AR index for the prediction of all-cause mortality at 1 year (9). In our cohort, the cumulative survival plot in relation to the severity of periAR and the AR index cutoff value (<25), respectively, was estimated by the Kaplan-Meier method. Survival in groups was compared with use of the log-rank test. To identify predictors of 1-year all-cause mortality after TAVI, a Cox proportional hazard model was applied. All tests were 2-sided; statistical significance was assumed when the null hypothesis could be rejected at $p < 0.05$.

Results

Baseline characteristics. In this study, 122 patients with severe, symptomatic aortic stenosis at high risk for open-heart surgery (age 81.7 ± 6.8 years, Society of Thoracic Surgeons mortality score: 7.3 ± 4.3%, logistic EuroSCORE 22.4 ± 13.0%) underwent TAVI by use of either the Medtronic CoreValve (79.5%) or the Edwards-SAPIEN prosthesis (20.5%). Baseline characteristics are summarized in Table 1. Echocardiographic assessment of the severity of periAR after TAVI demonstrated that moderate periAR persisted in 18 patients (14.8%), and severe periAR persisted in 2 patients (1.6%) despite correction maneuvers (Fig. 1).

Because the occurrence of moderate/severe periAR was considered clinically relevant, TAVI patients were divided into 2 groups according to the severity of periAR (none/mild vs. moderate/severe) for the comparison of baseline characteristics. In patients with moderate/severe periAR, both the logistic EuroSCORE (28.5 ± 15.0% vs. 21.2 ± 12.2%; $p = 0.05$) and the Society of Thoracic Surgeons mortality score (9.5 ± 4.4% vs. 6.8 ± 4.1%; $p = 0.021$) were significantly higher compared with patients without or only mild periAR. Furthermore, patients with moderate/severe periAR after the procedure suffered more frequently from previous myocardial infarction (40.0% vs. 9.8%; $p = 0.001$) and had a significantly lower left ventricular ejection fraction (45.1 ± 10.6% vs. 50.9 ± 10.8%; $p = 0.029$). The mean aortic annulus diameter was significantly larger (23.8 ± 1.6 mm vs. 22.7 ± 1.9 mm; $p = 0.022$), and the implantation depth at the site of the left-coronary (12.5 ± 5.0 mm vs. 8.8 ± 3.9 mm; $p < 0.001$) as well as of the noncoronary cusp (11.0 ± 4.5 mm vs. 8.1 ± 4.1 mm; $p = 0.005$) was significantly lower in patients suffering from moderate/severe periAR, compared with patients with none/mild periAR. The cover index was significantly higher in patients with none/mild periAR compared with patients with moderate/severe periAR: 16.0 ± 4.4% versus 13.5 ± 3.6% ($p = 0.020$).

Treatment of periAR. Post-dilation of the valve prosthesis was performed in 12 of 27 patients with moderate/severe periAR immediately after valve deployment. The final aortogram after correction maneuvers showed that periAR could be reduced for at least 1 grade in 9 patients by post-dilation only. In 2 patients with severe periAR, a second prosthesis had to be implanted in "valve-in-valve technique" due to deep implantation (Fig. 1). Despite post-dilation, severe periAR remained unchanged in 2 inoperable patients with heavily calcified cusps of the native aortic valve.

Echocardiographic assessment of periAR. There were no cases of more than trivial transvalvular AR. Transesophageal echocardiography, which predominantly guided TAVI in this cohort, revealed that 26 patients (21.3%) had no signs of periAR, 76 patients (62.3%) had only mild periAR, whereas 18 patients (14.8%) and 2 patients (1.6%) suffered from moderate and severe post-procedural periAR, respectively—independent from the type of valve prosthesis. The grading of periAR by TEE at the end of the TAVI procedure strongly correlated with the final angiogram after valve deployment ($r = 0.80$; $p < 0.001$) (Fig. 2).

Hemodynamic assessment of periAR. Simultaneous measurement of the left ventricular and aortic pressure showed a stepwise decrease of the gradient between LVEDP and the DBP in the aorta with increasing degree of periAR ($p < 0.001$) immediately after valve implantation (Table 2).

To adjust the end-diastolic gradient for the systemic blood pressure level, the AR index was calculated as proposed recently in the Bonn cohort (9) according to the following formula: AR index = ([DBP − LVEDP]/systolic blood pressure) × 100. The AR index was 29.4 ± 6.3 in patients without periAR and decreased with increasing severity of periAR from 25.1 ± 6.4 in patients with mild periAR, to 16.8 ± 5.3 in patients with moderate periAR, and to 4.3 ± 1.4 in patients with severe periAR ($p < 0.001$).

Clinical outcomes after TAVI according to the severity of periAR. Of 122 patients, 11 (9.0%) died within the first 30 days after TAVI; 32 of 122 patients (26.2%) died during follow-up of 1 year. Mean follow-up time in survivors was 672 ± 444 days with a follow-up rate of 100%.

In patients with moderate/severe periAR as assessed by post-procedural TEE, a 1-year mortality of 60.0% (12 of 20) was observed, compared with 19.6% (20 of 102) in patients with none/mild periAR ($p < 0.001$) (Fig. 3A). In univariate regression analysis, moderate/severe periAR was related to 1-year mortality after TAVI (hazard ratio 4.2, 95% confidence interval: 2.1 to 8.6; $p < 0.001$) (Table 3).

AR index and outcome. An AR index of <25 could be reconfirmed in this independent TAVI cohort as the optimum cutoff value (with the maximum sum out of sensitivity and specificity) for the prediction of moderate/severe periAR (sensitivity 100%, specificity 68%; area under the curve 0.89; $p < 0.001$) and for the prediction of 1-year mortality (sensitivity 73%, specificity 66%; area under the curve 0.68; $p = 0.002$). Patients with AR index <25 had a

Table 1. Baseline Characteristics According to Degree of Periprosthetic Regurgitation as Assessed by TEE After the Procedure

	All Patients (N = 122)	None/Mild PeriAR (n = 102)	Moderate/Severe PeriAR (n = 20)	p Value
Age (yrs)	81.7 ± 6.8	81.5 ± 6.9	82.5 ± 6.1	0.57
Male	65 (53.3)	51 (50.0)	14 (70.0)	0.11
Logistic EuroSCORE (%)	22.4 ± 13.0	21.2 ± 12.2	28.5 ± 15.0	0.05
STS score: mortality (%)	7.3 ± 4.3	6.8 ± 4.1	9.5 ± 4.4	0.012
Body mass index (kg/m^2)	26.3 ± 4.6	26.8 ± 4.5	24.2 ± 4.1	0.021
Height (cm)	165.6 ± 10.5	165.4 ± 10.3	166.7 ± 11.2	0.62
Weight (kg)	72.3 ± 15.1	73.3 ± 15.1	67.6 ± 14.9	0.13
Coronary artery disease	76 (62.3)	60 (58.8)	16 (80.0)	0.10
Peripheral artery disease	30 (24.6)	23 (22.5)	7 (35.0)	0.31
Previous MI	18 (14.8)	10 (9.8)	8 (40.0)	0.001
Previous PCI	34 (27.9)	26 (25.5)	8 (40.0)	0.21
Previous CABG	37 (30.3)	31 (30.4)	6 (30.0)	0.93
Previous stroke	20 (16.4)	14 (13.7)	6 (30.0)	0.08
Chronic renal failure	48 (39.3)	38 (37.3)	10 (50.0)	0.58
COPD	42 (34.4)	32 (31.4)	10 (50.0)	0.12
Pulmonary hypertension	17 (13.9)	12 (11.8)	5 (25.0)	0.14
LVEF (%)	49.9 ± 10.9	50.9 ± 10.8	45.1 ± 10.6	0.029
Aortic valve area (cm^2)	0.64 ± 0.19	0.63 ± 0.19	0.71 ± 0.19	0.14
Mean aortic gradient (mm Hg)	44.2 ± 15.8	45.7 ± 16.4	38.0 ± 11.2	0.11
Pre-procedural AR				0.16
None	60 (49.2)	54 (53.0)	6 (30.0)	
Mild	51 (41.8)	40 (39.2)	11 (55.0)	
Moderate	11 (9.0)	8 (7.8)	3 (15.0)	
Severe	0 (0)	0 (0)	0 (0)	
Aortic annulus diameter (mm)	22.9 ± 1.9	22.7 ± 1.9	23.8 ± 1.6	0.022
Aortic annulus ≥26 mm	10 (8.2)	6 (5.9)	4 (20.0)	0.040
Balloon valvuloplasty size (mm)	23.0 ± 1.8	22.9 ± 1.9	23.5 ± 1.6	0.28
Implantation depth NCC (mm)	8.6 ± 4.3	8.1 ± 4.1	11.0 ± 4.5	0.005
Implantation depth LCC (mm)	9.4 ± 4.3	8.8 ± 3.9	12.5 ± 5.0	<0.001
Prosthesis type				0.20
CoreValve 26 mm	45 (36.9)	37 (36.3)	8 (40.0)	
CoreValve 29 mm	52 (42.6)	42 (41.2)	10 (50.0)	
Edwards-SAPIEN 23 mm	9 (7.4)	9 (8.8)	0 (0)	
Edwards-SAPIEN 26 mm	16 (13.1)	14 (13.7)	2 (10.0)	
Cover index (%)*	15.5 ± 4.4	16.0 ± 4.4	13.5 ± 3.6	0.020
Access site				0.37
Transfemoral	119 (97.5)	100 (98.0)	19 (95.0)	
Trans-subclavian	1 (0.8)	1 (1.0)	0 (0)	
Transapical	2 (1.7)	1 (1.0)	1 (5.0)	

Values are mean ± SD or n (%). *According to the definition of Détaint et al. (14): cover index = (prosthesis size − annulus diameter)/prosthesis size.

AR = aortic regurgitation; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; EuroSCORE = European system for cardiac operative risk evaluation score; LCC = left-coronary cusp; MI = myocardial infarction; NCC = noncoronary cusp; PCI = percutaneous coronary intervention; periAR = periprosthetic aortic regurgitation; STS = Society of Thoracic Surgeons.

significantly increased 1-year mortality risk compared with patients with AR index ≥25 (43.3% vs. 14.3%: $p < 0.001$) (Fig. 3B).

As shown in the development cohort from Bonn (9), the calculation of the AR index was particularly useful in patients with none/mild periAR and provided complementary prognostic information ($p = 0.04$): in patients with none/mild periAR, an AR index ≥25 was related to a 1-year mortality rate of 14.3% (10/70), whereas an AR index <25 was associated with a more than 2-fold higher 1-year mortality rate of 31.3% (10 of 32), respectively. All patients suffering from moderate/severe periAR after TAVI had an AR index <25 associated with a very poor prognosis and a mortality rate of 60.0% (12 of 20) (Fig. 4).

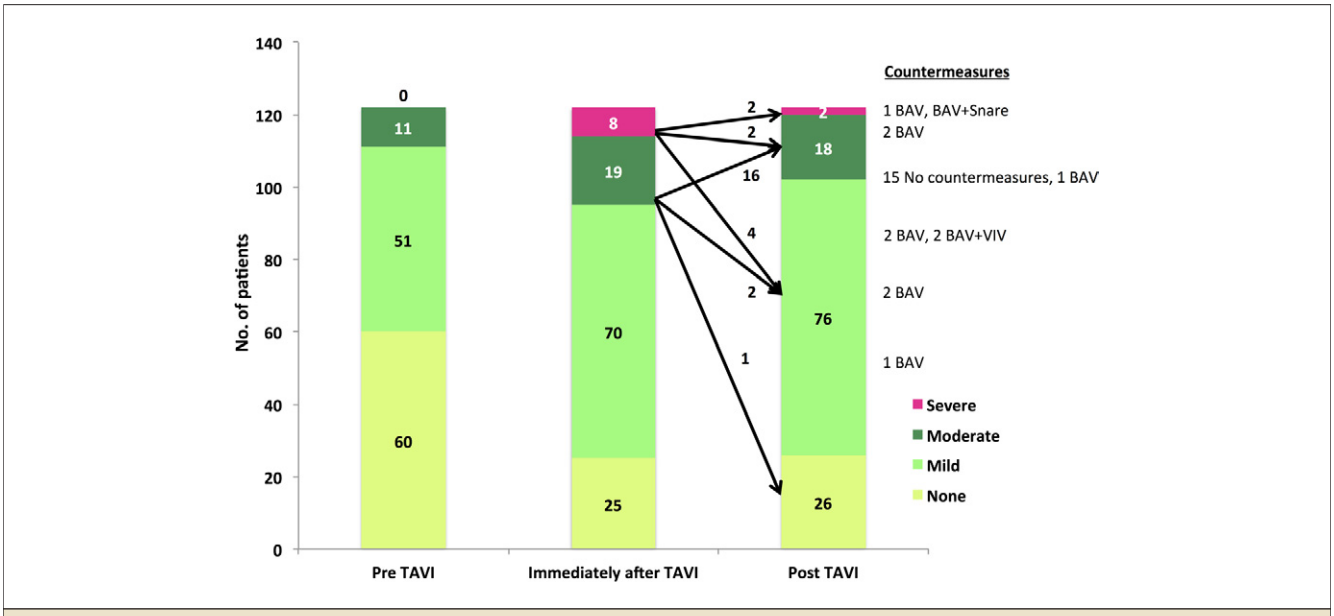

Figure 1. Incidence and Severity of Periprosthetic Aortic Regurgitation

The prevalence of AR before and periprosthetic aortic regurgitation (periAR) after transcatheter aortic valve implantation (TAVI) with the respective countermeasures. Absolute frequencies are given. BAV = balloon valvuloplasty; Snare = snare catheter used; VIV = valve-in-valve implantation.

Discussion

In this independent TAVI cohort, we were able to validate the AR index as a new hemodynamic parameter for the measurement of the degree of periAR and its predictive value for clinical outcome. This hemodynamic parameter strongly predicted 1-year mortality after TAVI—independent of the severity of periAR—and provided additional prognostic information beyond the echocardiographically assessed severity of periAR, because it was able to further stratify TAVI patients with none or only mild periAR and identified patients with increased risk for adverse outcome.

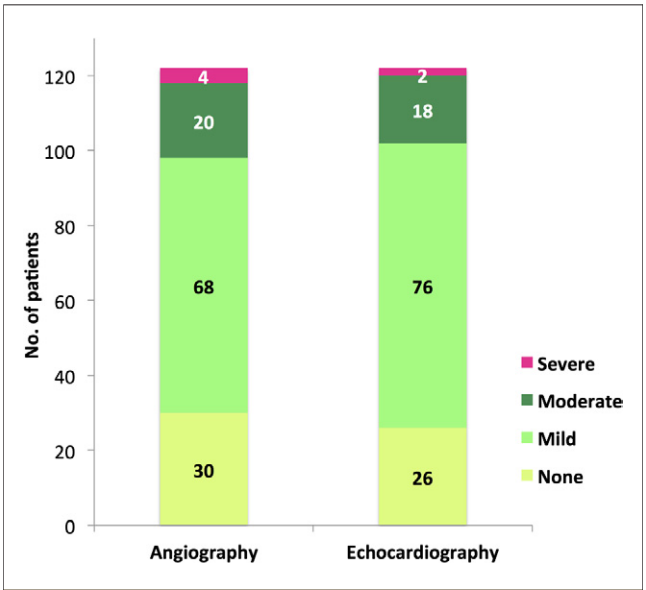

Figure 2. Assessment of the Degree of Periprosthetic Aortic Regurgitation After TAVI by Angiography and Echocardiography

Incidence of periprosthetic aortic regurgitation after transcatheter aortic valve implantation (TAVI) as assessed by angiography and transesophageal echocardiography in accordance with Valve Academic Research Consortium criteria.

Occurrence of periAR after TAVI. In this validation cohort, it was confirmed that severely impaired left ventricular ejection fraction, cover index as surrogate for prosthesis/annulus mismatch (14), and prosthesis implantation depth are major predictors for the occurrence of moderate/severe periAR after TAVI (9,12–16,23). The TAVI was performed under general anesthesia and guided by intraprocedural TEE. In contrast, in the development cohort from Bonn, most of the TAVI procedures were performed under local anesthesia and predominantly guided by angiography and hemodynamic parameters. Furthermore, patients from the Bonn cohort underwent TAVI with use of the Medtronic CoreValve prosthesis only, whereas in 20.5% of the patients in the Leicester cohort, the Edwards-SAPIEN prosthesis was used. Interestingly, the incidence of moderate/severe periAR (Leicester: 16.4%, Bonn: 15.1%) was comparable between both cohorts. We observed a trend toward less moderate/severe periAR in patients with use of the Edwards-SAPIEN prosthesis, although not significant compared with use of the Medtronic CoreValve prosthesis (8.0% vs. 18.8%; $p = 0.20$). However, this subgroup analysis is limited by the small sample size of Edwards-SAPIEN patients in our cohort.

Table 2. Hemodynamic Parameters After TAVI According to the Degree of Periprosthetic Regurgitation

	All Patients (N = 122)	No PeriAR (n = 27)	Mild PeriAR (n = 75)	Moderate PeriAR (n = 18)	Severe PeriAR (n = 2)	p Value
Aortic systolic pressure (mm Hg)	118.3 ± 24.5	119.8 ± 28.0	120.2 ± 24.7	111.3 ± 11.5	83.0 ± 11.3	0.12
Aortic diastolic pressure (mm Hg)	49.1 ± 9.8	51.9 ± 8.6	49.6 ± 10.0	44.7 ± 7.2	31.0 ± 5.7	0.007
LVEDP (mm Hg)	20.1 ± 6.4	16.9 ± 4.9	19.8 ± 5.9	25.9 ± 7.0	27.5 ± 5.0	<0.001
End-diastolic gradient (mm Hg)	29.1 ± 9.7	35.2 ± 7.8	29.8 ± 8.3	18.9 ± 6.0	3.5 ± 0.7	<0.001
AR index	24.6 ± 7.6	29.4 ± 6.3	25.1 ± 6.4	16.8 ± 5.3	4.3 ± 1.4	<0.001

Values are mean ± SD.
LVEDP = left ventricular end-diastolic pressure; periAR = periprosthetic aortic regurgitation; TAVI = transcatheter aortic valve implantation.

PeriAR and outcome after TAVI. Recent analyses underline the importance of more-than-mild post-procedural periAR for short- and long-term outcome (9,10,16). We were able to confirm these findings in our cohort and demonstrated that a moderate/severe periAR, which occurred in 15% to 16% of patients, was strongly related to both 30-day (Leicester: 30.0%, Bonn: 22.7%) and 1-year mortality (Leicester: 60.0%, Bonn: 63.6%). Interestingly, in our TAVI cohort, patients suffering from moderate/severe periAR (and subsequently worse short-term outcome) had a significantly lower body mass index. This association might be a potential confounder of—or at least partly contribute to—the hypothesis that a low body mass index is an independent predictor of mortality in TAVI patients (25).

Moderate periAR was tolerated in 15 patients without corrective measures, which might be explained—at least in part—by inclusion of early experience patients with underestimation of the negative impact of more-than-mild periAR. However, the incidence of moderate/severe periAR in our study cohort (16%) is in line with recently published reports (between 10% and 28%) (8–17).

AR index and outcome. In addition, the AR index was a strong predictor of 1-year mortality risk, even after adjustment for the severity of periAR, indicating the independent relevance of objectively assessed hemodynamic changes in the long run.

Our data clearly underscore that all efforts must be taken to avoid moderate/severe periAR in TAVI patients. In patients with moderate/severe periAR after valve deployment, corrective measures—such as balloon valvuloplasty for not fully expanded stent frames, valve reposition with snare catheters for too-deep implantation depth, or "valve-in valve" technique for suboptimal deployment—play a crucial

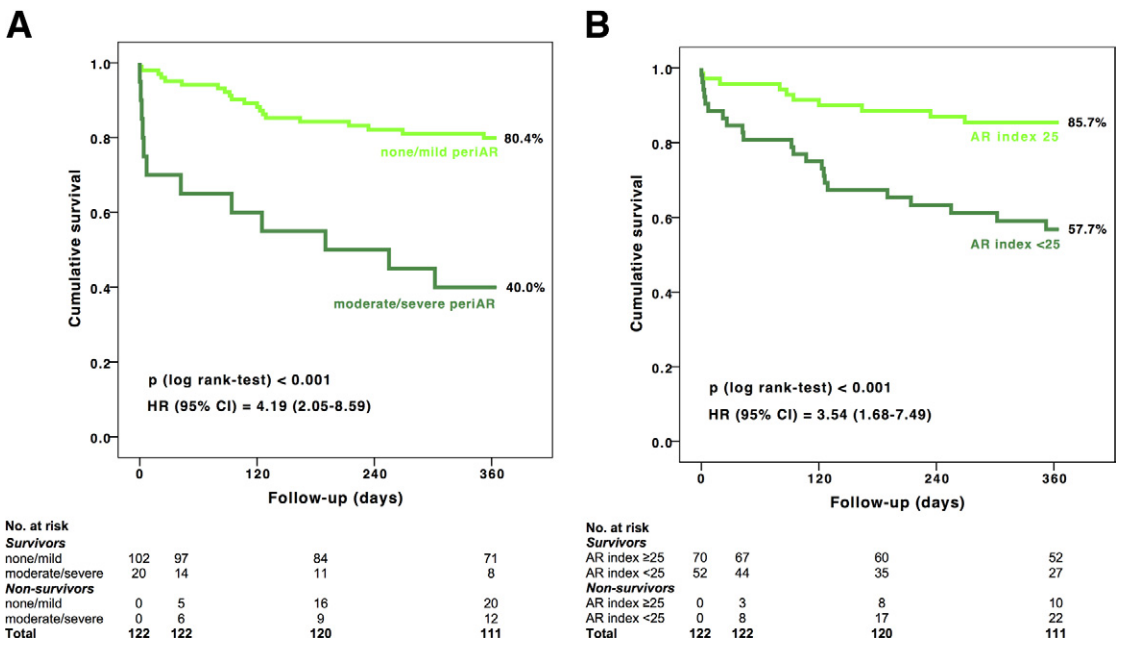

Figure 3. 1-Year Mortality According to the Severity of PeriAR and the Aortic Regurgitation Index

Cumulative survival (freedom from all-cause mortality) according to the severity of periprosthetic aortic regurgitation (periAR) **(A)** as assessed by transesophageal echocardiography and aortic regurgitation index cutoff value **(B)** developed in the Bonn cohort (9). CI = confidence interval; HR = hazard ratio.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 8, 2012
AUGUST 2012:858–65

role to decrease the severity of periAR and thereby increase survival (9,13). We could demonstrate that the AR index is a simple and reproducible hemodynamic measure for the precise quantification of periAR and can guide periprocedural decision making.

Quantification of periAR after TAVI. Because precise quantification of the degree of periAR remains challenging despite the recently suggested VARC criteria—independent of whether using a qualitative angiographic or semiquantitative echocardiographic approach (11–13,18–22)—we are in need of an objective parameter, such as the AR index. This is especially applicable for the acute implantation situation with sub-ideal conditions for echocardiographic examination, especially when the procedure is not performed under general anesthesia, or in patients with chronic renal failure with sparse use of contrast media. In both the development cohort from Bonn and the validation cohort from Leicester, we were able to demonstrate that the AR index as hemodynamic parameter is easy to quantify and allows an objective, fast, and reproducible assessment of the degree of periAR directly during the procedure with the possibility to undertake effective measures to decrease periAR and therefore increase survival.

Study limitations. The validity of the AR index could be confirmed in this independent cohort of another high-volume TAVI center, suggesting that this finding can be generalized. Univariate regression analysis only has been presented, because the event count was not sufficient to support multivariate analysis with inclusion of all 7 mortality predictors in our study, and thus a multivariate model would have been overfitted. However, an AR index below the cutoff of 25 was an independent predictor for 1-year mortality when multivariate Cox regression analysis was performed. A prospective multicenter trial might be needed to further verify these results. Furthermore, it has to be tested whether our results apply to transcatheter heart valve types other than the currently approved CoreValve or Edwards-SAPIEN prosthesis.

Table 3. Univariate Cox Regression Analysis of the Association Between Clinical Characteristics and 1-Year Mortality

	HR (95% CI)	p Value
Moderate/severe periAR	4.2 (2.1–8.6)	<0.001
AR index cutoff value	3.5 (1.7–7.5)	<0.001
STS score ≥10	2.9 (1.4–6.2)	0.005
Logistic EuroSCORE ≥20	2.8 (1.3–6.0)	0.006
Pulmonary hypertension	2.5 (1.1–5.6)	0.024
LVEF ≤35%	2.5 (1.1–5.7)	0.036
Chronic renal failure	2.2 (1.0–5.0)	0.05

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

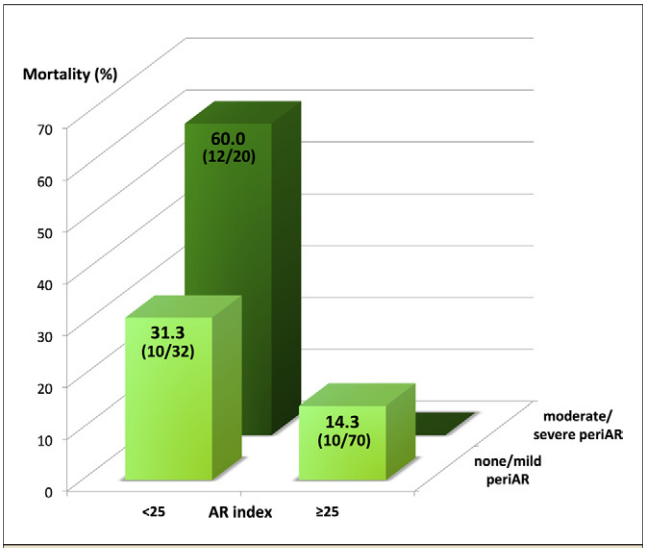

Figure 4. 1-Year Mortality According to Severity of periprosthetic AR and the AR Index

One-year all-cause mortality (in percentage) according to the severity of periprosthetic aortic regurgitation (AR) (none/mild vs. moderate/severe) and the AR index cutoff value.

Conclusions

The AR index is strongly associated with periprosthetic AR after TAVI, predicts 1-year mortality, and provides prognostic information beyond the degree of AR as demonstrated in this validation cohort.

Reprint requests and correspondence: Dr. Jan Kovac, Department of Cardiology, Glenfield University Hospital, Groby Road, Leicester LE3 9QP, United Kingdom. E-mail: jankovac2@hotmail.com.

REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364:2187–98.
3. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006–8.
4. Grube E, Laborde JC, Gerckens U, et al. Percutaneous implantation of the CoreValve self-expanding valve prosthesis in high-risk patients with aortic valve disease: the Siegburg first-in-man study. Circulation 2006;114:1616–24.
5. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. Circulation 2009;119:3009–16.
6. Rodés-Cabau J, Webb JG, Cheung A, et al. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010;55: 1080–90.

7. Wenaweser P, Pilgrim T, Kadner A, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. J Am Coll Cardiol 2011;58:2151–62.
8. Zahn R, Gerckens U, Grube E, et al. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32:198–204.
9. Sinning JM, Hammerstingl C, Vasa-Nicotera M, et al. Aortic regurgitation index defines severity of periprosthetic regurgitation and predicts outcome in patients after transcatheter aortic valve implantation. J Am Coll Cardiol 2012;59:1134–42.
10. Tamburino C, Capodanno D, Ramondo A, et al. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299–308.
11. Sherif MA, Abdel-Wahab M, Beurich HW, et al. Haemodynamic evaluation of aortic regurgitation after transcatheter aortic valve implantation using cardiovascular magnetic resonance. EuroIntervention 2011;6:57–63.
12. Schultz CJ, Tzikas A, Moelker A, et al. Correlates on MSCT of paravalvular aortic regurgitation after transcatheter aortic valve implantation using the Medtronic CoreValve prosthesis. Catheter Cardiovasc Interv 2011;78:446–55.
13. Takagi K, Latib A, Al-Lamee R, et al. Predictors of moderate-to-severe paravalvular aortic regurgitation immediately after CoreValve implantation and the impact of postdilatation. Catheter Cardiovasc Interv 2011;78:432–43.
14. Détaint D, Lepage L, Himbert D, et al. Determinants of significant paravalvular regurgitation after transcatheter aortic valve: implantation impact of device and annulus discongruence. J Am Coll Cardiol Intv 2009;2:821–7.
15. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol 2009;53:1883–91.
16. Abdel-Wahab M, Zahn R, Horack M, et al. Aortic regurgitation after transcatheter aortic valve implantation: incidence and early outcome. Results from the German transcatheter aortic valve intervention registry. Heart 2011;97:899–906.
17. Sinning JM, Ghanem A, Steinhäuser H, et al. Renal function as predictor of mortality in patients after percutaneous transcatheter aortic valve implantation. J Am Coll Cardiol Intv 2010;3:1141–9.
18. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the valve academic Research Consortium. Eur Heart J 2011;32:205–17.
19. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J Am Soc Echocardiogr 2009;22:975–1014.
20. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. Eur Heart J 2011;32:2189–214.
21. Croft CH, Lipscomb K, Mathis K, et al. Limitations of qualitative angiographic grading in aortic or mitral regurgitation. Am J Cardiol 1984;53:1593–8.
22. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. Am J Cardiol 1964;14:437–47.
23. Sherif MA, Abdel-Wahab M, Stöcker B, et al. Anatomic and procedural predictors of paravalvular aortic regurgitation after implantation of the Medtronic CoreValve bioprosthesis. J Am Coll Cardiol 2010;56:1623–9.
24. Jilaihawi H, Chin D, Spyt T, et al. Prosthesis-patient mismatch after transcatheter aortic valve implantation with the Medtronic-Corevalve bioprosthesis. Eur Heart J 2010;31:857–64.
25. Wenaweser P, Pilgrim T, Roth N, et al. Clinical outcome and predictors for adverse events after transcatheter aortic valve implantation with the use of different devices and access routes. Am Heart J 2011;161:1114–24.

Key Words: CoreValve ■ Edwards-SAPIEN ■ paravalvular leakage ■ periprosthetic aortic regurgitation ■ TAVI.