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Impact of Post-Procedural Aortic Regurgitation on Mortality After Transcatheter Aortic Valve Implantation

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Objectives The goal of the study was to clarify the impact of post-procedural aortic regurgitation (post-AR) grade 2/4 on clinical outcomes.

Background Post-AR >2/4 is known to be associated with poor short- to midterm outcome after transcatheter aortic valve implantation (TAVI).

Methods We compared clinical outcomes in 400 consecutive TAVI recipients according to post-AR grade: grade 0 or 1 (group 1 = 74.8%), grade 2 (group 2 = 22.2%), or grade 3 or 4 (group 3 = 3.0%).

Results The mean age was similar in the 3 groups (83.4 ± 6.1 years) as was the logistic EuroSCORE (22.5 ± 11.4%, 24.5 ± 11.6%, and 21.5 ± 9.4%, p = 0.28) and annulus size (22.0 ± 1.8, 22.2 ± 2.1, and 22.5 ± 2.1 mm, p = 0.53). The Edwards valve was most frequently used in group 1 compared with groups 2 and 3 (89.3%, 78.7%, and 83.3%, p = 0.03), and the implanted valve size was similar in all groups (25.6 ± 2.0, 25.4 ± 2.2, and 25.5 ± 2.2 mm, respectively, p = 0.69). Post-dilation was required more frequently in group 3 (4.7%, 24.1%, and 50.0%, respectively, p < 0.01). Post-procedural increase in mitral regurgitation was in line with the post-AR grade (0.78 ± 0.73, 1.22 ± 0.80, and 1.89 ± 0.78, respectively, p < 0.01). Despite the absence of difference in 30-day mortality, longer-term outcome was significantly poorer in patients with AR grade 2 than in those with AR grade 0 or 1 (log-rank p < 0.01), albeit better than in patients with AR grade 3 or 4 (p = 0.04), regardless of TAVI type and left ventricular function. Post-AR ≥2/4 was also identified as an independent predictor of mid- to long-term mortality (hazard ratio: 1.68, 95% confidence interval: 1.21 to 1.44, p < 0.01).

Conclusions Post-AR grade 2/4 after TAVI is associated with worse outcome compared with grade 0 or 1. Careful valve selection and post-dilation when required to avoid post-AR grade 2 may contribute to improved clinical outcome after TAVI. (J Am Coll Cardiol Intv 2012;5:1247–56) © 2012 by the American College of Cardiology Foundation

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Transcatheter aortic valve implantation (TAVI) has emerged as a viable therapeutic option for patients with severe symptomatic aortic stenosis (AS) who are ineligible or at high-risk for conventional surgical aortic valve replacement (1–3). Although this technique has reached relative maturity, further optimization of patient selection and device implantation is necessary. TAVI is a procedure whereby a stent-framed bioprosthesis is placed (positioned, deployed) by compression and without resection of the native aortic valve. This may result in a gap being created between the implanted device and the native aortic valve in instances where the native valve or its annulus is calcified, thus leading to post-procedural aortic regurgitation (AR) (4). Significant post-procedural AR (grade ≥2/4) after TAVI was recently identified as a predictor of 1-year mortality (5). However, the differences in terms of impact on the clinical outcome between post-procedural AR grade 2 and grade 0 or 1 were not sufficiently documented. Post-dilation has been proposed to reduce the degree of post-procedural AR. However, this strategy may increase the risk of aortic rupture, central valvular regurgitation, accelerated degenerative process, or possibly stroke. Given the potential complications involved, the degree of AR warranting post-dilation should be carefully determined.

The objective of this study was to clarify the impact of each grade of post-procedural AR on clinical outcomes and provide guidance for optimal valve size selection and post-dilation strategy.

Abbreviations and Acronyms

AR = aortic regurgitation
AS = aortic stenosis
CI = confidence interval
CT = computed tomography
dAR = degree of aortic regurgitation
Diam-TEE = annulus diameter measured by transesophageal echocardiography
HR = hazard ratio
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
TAVI = transcatheter aortic valve implantation
TEE = transesophageal echocardiography

Methods

Study population and design. From October 2006, all patients with severe symptomatic AS treated with TAVI at our institution were prospectively included in our TAVI database. Patients with severe symptomatic AS (valve area ≤1.0 cm^2) were considered candidates for TAVI if they had a logistic European System for Cardiac Operative Risk Evaluation score (EuroSCORE) >20%, if surgery was deemed to carry excessive risk due to significant comorbidities, or if other risk factors not captured by these scoring systems (e.g., porcelain aorta) were present. The decision to proceed with TAVI was discussed by a dedicated heart team, including experienced clinical and interventional cardiologists, cardiovascular surgeons, and anesthesiologists. All patients selected for TAVI underwent screening, physical examination, transthoracic and transesophageal echocardiography (TEE), baseline laboratory tests, and coronary angiography. Assessment of the aortic annulus size was performed by TEE and/or multidetector computed tomography (CT).

Between October 2006 and October 2011, a total of 424 patients were included in our TAVI database. TEE-guided valve sizing was performed during the early stages of our experience, and CT-guided sizing has been progressively introduced since 2009.

Twenty-four patients were excluded from this analysis because they either did not receive TAVI or died during or within 24 h of the procedure due to reasons that were obviously not related to post-procedural AR.

Procedural characteristics and clinical outcomes were compared in the remaining 400 consecutive TAVI recipients according to post-procedural AR grades: grade 0 or 1 (group 1), grade 2 (group 2), or grade 3 or 4 (group 3).

All patients agreed to participate in the study, and written informed consent was obtained in all cases.

Vascular access and valve selection. Patients were selected to undergo TAVI via the transfemoral approach or alternative approaches depending on the size, calcification and tortuosity of the iliofemoral arterial access. The type of bioprosthesis was selected according to the diameter of the aortic annulus which, in the early phases of our experience, was systematically measured using TEE (Diam-TEE). More recently, the mean annulus diameter has been calculated using multidetector CT (mDiam-CT) (6). The Edwards valve (Edwards Lifesciences, Irvine, California) was used in patients with a diameter of 18 to 24.5 mm and the CoreValve (Medtronic, Minneapolis, Minnesota) was selected for annular diameters of 20 to 26.5 mm via the transfemoral approach. For historical reasons (the Edwards valve was first introduced in 2006), the Edwards valve was used preferentially in patients with an annulus diameter of 20 to 24.5 mm, who were amenable to treatment with either valve. The CoreValve prosthesis was implanted in patients whose annulus size was >24.5 mm, or patients with borderline iliofemoral access when 18- and 19-F Edwards sheaths were not available.

The trans-subclavian or transaortic approach was used as an alternative in cases of unsuitable femoral arterial access in recipients of the CoreValve with annular diameters of 20 to 28 mm, and the transapical, trans-subclavian, or transaortic route as the alternative to suboptimal femoral access with the Edwards valve in patients with annular diameters of 18 to 26.5 mm.

Echocardiography. A detailed transthoracic echocardiography and TEE examination was performed in all cases during initial patient assessment by experienced echocardiographers by means of the Philips ie33 ultrasound system (Philips Medical, Amsterdam, the Netherlands) and a dedicated Philips probe. The aortic annulus diameter was

defined as the distance (in millimeters) between the hinge points of the aortic valve leaflets, and was measured in the long-axis view of the aortic valve at end-systole using TEE, according to published recommendations (7,8). In all cases, the diameter was measured 3 times, and the mean value was used for TEE valve sizing. The degree of pre- and post-procedural AR was measured with color Doppler using transthoracic echocardiography by 2 independent experienced echocardiographers, who were unaware of the procedural information according to current guidelines (8) and was translated into a semiquantitative grade as 0 = none, 1 = trivial, 2 = mild, 3 = moderate, and 4 = severe. All Doppler measurements were evaluated as the average of at least 3 cycles in patients with sinus rhythm or more than 5 cycles in those with atrial fibrillation. Consensus was obtained between 2 operators when there were discrepancies. In Kaplan-Meier survival analysis, we also evaluated the change in the degree of aortic regurgitation (dAR) in the groups as follows; "AR improved": (dAR = −2 or 3), "AR no or little change": (dAR = −1 to +1) and "AR worsened": (dAR =+2 or 3).

Procedures. Before TAVI, patients were on aspirin (75 to 160 mg) and clopidogrel (75 mg) daily, or were given a loading dose of clopidogrel (300 to 600 mg) before or immediately after the procedure. From January 2010, patients on warfarin were only administered a combination of aspirin and warfarin after TAVI. A bolus of intravenous heparin (70 IU/kg) was administered at the start of each procedure to achieve an activated clotting time of 250 to 300 s, and the activated clotting time was measured every 30 min thereafter. Transfemoral procedures were performed by experienced interventional cardiologists, and nontransfemoral procedures by a team of at least 1 cardiac surgeon and 1 interventional cardiologist according to our standard operating procedures, as previously described (9,10).

Post-procedural care. All patients were observed in the intensive care unit for at least 24 h after Edwards valve implantation or 72 h after CoreValve implantation (in patients without previous pacemaker placement). Dual antiplatelet therapy was continued for 6 months, and thereafter, aspirin was continued indefinitely.

Follow-up. After TAVI, all patients were assessed by a physician at 1, 3, 6, and 12 months post-operatively and annually thereafter. Additional follow-up data were collected through telephone interviews and contact with patients' family physicians, except for 1 patient lost during follow-up.

Endpoint definitions. The primary endpoint of this study was all-cause mortality over the duration of the study. All-cause mortality, combined 30-day safety endpoints, and device success as defined by the Valve Academic Research Consortium criteria (11), were also evaluated.

Statistical analysis. Quantitative variables are expressed as mean ± standard deviation, and qualitative variables as numbers and percentages. Comparison of quantitative variables was performed with a 1-way analysis of variance or Kruskal-Wallis test, depending on variable distribution. A Bonferroni test was used to define statistical differences between the groups. The Wilcoxon rank sum test was used to compare pre- and post-procedural MR in each group of paired data. The chi-square test or Fisher exact test was used to compare qualitative variables. Survival analyses were performed by Kaplan-Meier analysis.

A Cox regression analysis was used to examine the univariable association of clinical, procedural and echocardiographic variables with long-term mortality. Multivariable analysis, including all variables with p value ≤0.05 in the univariate analysis, was performed to determine the predictors of long-term mortality.

Statistical significance was defined as $p < 0.05$. The data were analyzed with SPSS Statistics 20.0 (SPSS, Chicago, Illinois).

Results

Between October 2006 and October 2011, TAVI was carried out in 400 of 424 patients initially scheduled to undergo this procedure at our institution.

Twenty-four patients were excluded from the current analysis: 11 patients who did not receive a valve (1 case of recurrent ventricular fibrillation after balloon valvuloplasty and before valve deployment; 1 abdominal aortic rupture before TAVI implantation; 1 case of failed crossing of a native valve with a bioprosthesis; 4 cases of failed arterial access, 4 cases of valve migration), 13 patients who died during or within 24 h of the procedure due to patently different reasons (1 left main occlusion, 3 annulus ruptures, 2 cardiogenic shocks during the procedure due to low left ventricular ejection fraction, 1 cerebrovascular accident, 2 cardiac tamponade, and 4 access site complications).

The remaining 400 patients received either the Edwards valve (n = 347) or the CoreValve Revalving system (n = 53). The cohort was divided into 3 groups according to the degree of post-procedural AR as follows: group 1: AR grade 0 or 1 (299 cases), group 2: AR grade 2 (89), and group 3: AR grade 3 or 4 (12), and the patient characteristics and clinical outcomes were compared. Post-procedural AR mostly consisted of paraprosthetic leak, and no central AR grade ≥2 was observed in this cohort.

Patient characteristics. The mean age of the entire population was 83.4 ± 6.1 years (Table 1). Congestive heart failure class III/IV was prevalent in 86.8%, coronary artery disease in 59.3%, previous coronary artery bypass grafting had been performed in 15.8%, and 63.0% of patients had significant renal dysfunction (estimated glomerular filtration rate <60 ml/min). The mean logistic EuroSCORE was 22.9 ±

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Table 1. Baseline Characteristics of the Study Population

	Total (N = 400)	Group 1 (n = 99)	Group 2 (n = 89)	Group 3 (n = 12)	p Value
Age, yrs	83.4 ± 6.1	83.0 ± 6.3	84.5 ± 5.4	82.8 ± 5.0	0.12
Male	194 (48.5)	143 (47.8)	43 (48.3)	8 (66.7)	0.44
Diabetes	92 (23.0)	68 (22.7)	19 (21.3)	5 (41.7)	0.29
Hyperlipidemia	193 (48.3)	152 (50.8)	34 (38.2)	7 (58.3)	0.09
Hypertension	276 (69.0)	200 (66.9)	68 (76.4)	8 (66.7)	0.23
Current smoker	21 (5.3)	11 (3.7)	9 (10.1)	1 (8.3)	0.05
NYHA functional class III/IV	347 (86.8)	256 (85.6)	79 (88.8)	12 (100)	0.29
Coronary artery disease	237 (59.3)	172 (57.5)	56 (62.9)	9 (75.0)	0.35
Previous CABG	63 (15.8)	48 (16.1)	13 (14.6)	2 (16.7)	0.88
Peripheral artery disease	127 (31.8)	94 (31.4)	26 (29.2)	7 (58.3)	0.12
Cerebrovascular disease	41 (10.3)	29 (9.7)	9 (10.1)	3 (25.0)	0.23
COPD	124 (31.0)	88 (29.4)	28 (31.5)	7 (58.3)	0.10
eGFR <60 ml/min.	249 (63.0)	177 (60.0)	64 (72.7)	8 (66.7)	0.09
Logistic EuroSCORE, %	22.3 (17.1–30.3)	22.2 (16.4–29.4)	24.9 (18.2–30.9)	21.1 (17.0–25.1)	0.28
STS score, %	7.9 (5.1–12.3)	7.4 (4.5–12.3)	8.3 (5.3–12.8)	8.3 (6.8–10.2)	0.81
Aortic valve area, cm^2	0.62 ± 0.15	0.63 ± 0.15	0.58 ± 0.13	0.51 ± 0.19	<0.01
Mean pressure gradient, mm Hg	47.8 ± 17.1	46.8 ± 15.5	48.8 ± 19.6	65.5 ± 26.2	0.08
LVEF <40%	115 (28.8)	78 (26.2)	33 (37.1)	3 (25.0)	0.13
Diam-TEE, mm	22.1 ± 1.9	22.0 ± 1.8	22.2 ± 2.1	22.5 ± 2.1	0.53
MDiam-CT, mm	23.6 ± 2.0	23.5 ± 2.0	24.1 ± 2.0	22.9 ± 2.7	0.27
Aortic regurgitation (0–4)	0.88 ± 0.71	0.92 ± 0.70	0.83 ± 0.74	0.42 ± 0.52	0.06
Mitral regurgitation (0–4)	1.02 ± 0.73	1.00 ± 0.71	1.07 ± 0.81	1.00 ± 0.71	0.73

Values are expressed as n (%), mean ± SD, or median (interquartile range).

BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CT = computed tomography; Diam-TEE = aortic annulus diameter measured by transesophageal echography; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

11.4%. The mean pressure gradient across the aortic valve was 47.8 ± 17.1 mm Hg, and the Diam-TEE was 22.1 ± 1.9 mm.

No significant differences were found in the baseline characteristics except for the aortic valve area (0.63 ± 0.15, 0.58 ± 0.13, and 0.51 ± 0.19 cm^2, $p < 0.01$). However, the aortic valve area did not emerge as a predictor of post-procedural AR ≥2 ($p = 0.19$). There were no significant differences between the groups in terms of gradient or baseline aortic and mitral regurgitation.

Procedural characteristics. The Edwards valve was implanted in 86.8% of patients and the CoreValve in 13.2% (Table 2). The mean valve size was 25.6 ± 2.1 mm, and the most commonly used device was the Edwards 26-mm valve (49.0%). Valve post-dilation was performed in 10.3% of cases, namely in 30 recipients of the Edwards valve and 8 recipients of the CoreValve (8.6% vs. 14.8%, $p = 0.15$). Two patients (0.5%) survived the acute phase after developing aortic annulus rupture (1 transfemoral and 1 transaortic case).

Following implantation, the mean aortic valve pressure gradient was 10.5 ± 4.4 mm Hg. Device success was achieved in 90.0% of cases, and the 30-day mortality rate was 9.5%.

The Edwards valve was most frequently used in group 1 (89.3%, 78.7%, and 83.3%, respectively, $p = 0.03$) although no significant differences in bioprosthesis size were recorded between the 3 groups (25.6 ± 2.0%, 25.4 ± 2.2%, and 25.5 ± 2.2%, respectively, $p = 0.69$).

The lower ratio between valve size and mDiam-CT was in line with the increase in the grade of post-procedural AR (1.11 ± 0.05, 1.09 ± 0.05, and 1.08 ± 0.21, respectively, $p = 0.03$). There was a similar trend for valve size and annulus diameter ratio as assessed by Diam-TEE and the grade of post-procedural AR (1.16 ± 0.07, 1.15 ± 0.06, and 1.13 ± 0.07, $p = 0.06$).

Thirty-six patients had AR grade 3 or 4 before post-dilation. Post-dilation was performed in 30 of these patients, and improvement was observed in 70% (21 patients; 6 into grade 0 or 1 and 15 into grade 2).

Of the 5 patients in whom annulus rupture occurred, 3 died during the procedure and were excluded from the study cohort. Analysis was carried out in the 2 remaining patients with annulus rupture who survived the acute phase (1 patient in group 1 and the other in group 2) (0.3%, 1.1%, and 0%, $p = 0.44$).

Interestingly, the post-procedural MR grade increased in parallel with the increase in the AR grade (0.78 ± 0.73,

Table 2. Procedural Characteristics of the Study Population

	Total (N = 400)	Group 1 (n = 299)	Group 2 (n = 89)	Group 3 (n = 12)	p Value
Edwards valve	347 (86.8%)	267 (89.3%)	70 (78.7%)	10 (83.3%)	0.03
Valve size, mm	25.6 ± 2.1	25.6 ± 2.0	25.4 ± 2.2	25.5 ± 2.2	0.69
Edwards 23 mm	127 (31.8%)	89 (29.8%)	34 (38.2%)	4 (33.3%)	0.03
26 mm	196 (49.0%)	155 (51.8%)	35 (39.3%)	6 (50.0%)	
29 mm	24 (6.0%)	23 (7.7%)	1 (1.1%)	0	
CoreValve 26 mm	11 (2.8%)	7 (2.3%)	4 (4.5%)	0	
29 mm	39 (9.8%)	22 (7.4%)	15 (16.9%)	2 (16.7%)	
31 mm	3 (0.8%)	3 (1.0%)	0	0	
Valve/Diam-TEE ratio	1.15 ± 0.07	1.16 ± 0.07	1.15 ± 0.06	1.13 ± 0.07	0.06
Valve/mDiam-CT ratio	1.10 ± 0.05	1.11 ± 0.05	1.09 ± 0.05	1.08 ± 0.21	0.03
	(n = 180)	(n = 148)	(n = 30)	(n = 2)	
Post-dilation	38 (10.3%)	13 (4.7%)	19 (24.1%)	6 (50.0%)	<0.01
Annulus rupture (survived)	2 (0.5%)	1 (0.3%)	1 (1.1%)	0	0.44
Post-implantation					
Mean pressure gradient, mm Hg	10.5 ± 4.4	10.6 ± 4.6	10.5 ± 3.8	9.3 ± 3.9	0.53
LVEF, %	54.7 ± 12.3	55.2 ± 12.2	53.1 ± 12.8	54.7 ± 19.9	0.44
Mitral regurgitation (0–4)	0.91 ± 0.78	0.78 ± 0.73	1.22 ± 0.80	1.89 ± 0.78	<0.01* 0.03†
Pacemaker	26 (7.9%)	16 (6.6%)	9 (12.0%)	1 (8.3%)	0.32
Acute kidney injury	36 (9.0%)	22 (7.4%)	12 (13.5%)	2 (16.7%)	0.13
Major vascular complication	35 (8.8%)	22 (7.4%)	11 (12.4%)	2 (16.7%)	0.21
Device success	372 (90.0%)	286 (95.7%)	86 (96.6%)	0	<0.01
30-Day mortality	38 (9.5%)	23 (7.7%)	13 (14.6%)	2 (16.7%)	0.10
30-Day combined safety endpoint	82 (20.5%)	54 (18.1%)	24 (27.0%)	4 (33.3%)	0.10
Hospital stay, days	9.5 (7.0–14.0)	10.0 (8.0–15.0)	9.0 (7.0–12.0)	13 (7.0–24.5)	0.19

Values are expressed as n (%), mean ± SD, or median (interquartile range). *p Value <0.001 between group 1 and 2, and group 1 and 3 (Bonferroni test). †p value 0.029 between group 2 and 3 (Bonferroni test).

Abbreviations as in Table 1.

1.22 ± 0.80, and 1.89 ± 0.78, $p < 0.01$ [group 1 vs. 2 and 1 vs. 3], $p = 0.03$ [group 2 vs. 3]) (Fig. 1). Significant improvement between pre- and post-procedural MR was observed in group 1 ($p < 0.01$): however, there was no significant improvement in group 2 ($p = 0.19$) and aggravation of MR was recorded in group 3 ($p = 0.05$).

At 30 days, there were no significant differences in acute kidney injury, major vascular complications, mortality, and combined safety endpoints.

Impact of post-procedural AR on long-term survival after TAVI. The median follow-up period of this cohort was 297 days (interquartile range: 101 to 607). In total, 109 patients (64 in group 1, 36 in group 2, and 9 in group 3) died during the follow-up period. The cumulative incidence of mortality at 2 years was 28.0%, 40.4%, and 75.0%, respectively. The impact of post-procedural AR on long-term mortality was evaluated.

Patients in group 3 had worse outcomes compared with those in group 1 (log-rank $p < 0.01$) and group 2 (log-rank $p = 0.04$) (Fig. 2A). Importantly, group 2 had a significantly worse outcome compared to group 1 (log-rank $p < 0.01$) (Fig. 2A). The same findings were consistently observed in recipients of the Edwards valve (Fig. 2B) and the CoreValve (Fig. 2C) alike, and in patients with ≥40% (Fig. 2D) left ventricular ejection fraction (LVEF) as in those with <40% LVEF (Fig. 2E). In group 2 (post-procedural AR grade 2), the impact of pre-procedural AR was analyzed, and patients with no pre-procedural AR had worse outcome compared with those who had pre-procedural AR (Fig. 3, log-rank $p = 0.01$).

The impact of the change in the grade of AR (dAR: difference between pre- and post-procedural AR grade) was also evaluated (Fig. 4). The increase in dAR (i.e., worsening of AR) also had a worse impact on mortality (log-rank $p < 0.01$).

Predictors of long-term mortality. Predictors of long-term mortality were evaluated. Following adjustment for other variables, significant post-procedural AR (grade ≥2) (hazard ratio [HR]: 1.70, 95% confidence interval [CI]: 1.13 to 2.56, $p < 0.01$), conversion to open heart surgery (HR: 5.98, 95% CI: 2.61 to 13.70, $p < 0.01$), major stroke (HR: 4.51, 95% CI: 1.90 to 10.71, $p = 0.01$), acute kidney injury (HR: 2.19, 95% CI: 1.21 to 3.95, $p = 0.01$), major vascular complication (HR: 1.73, 95% CI: 1.00 to 3.01, $p = 0.05$), transfusion ≥4 (HR: 2.21, 95% CI: 1.17 to 4.17, $p = 0.01$), and logistic EuroSCORE (HR: 1.01, 95% CI: 1.01

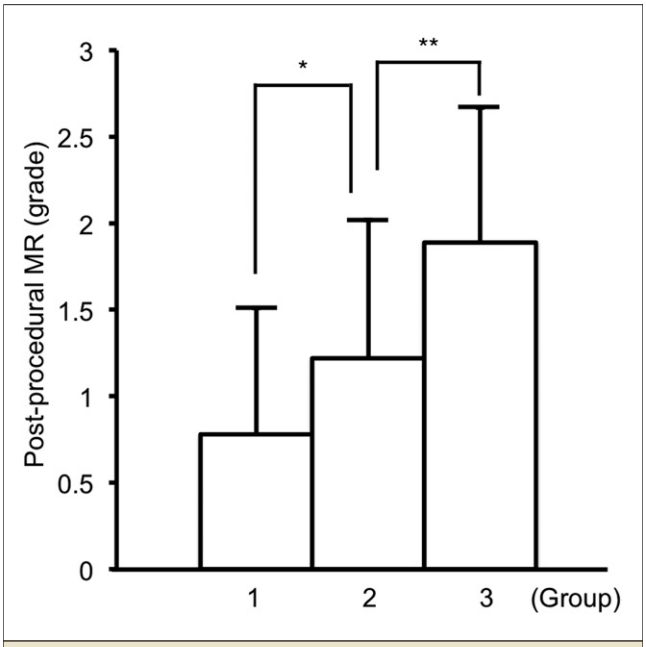

Figure 1. Post-Procedural MR and Post-Procedural AR

The grade of post-procedural MR in each group is shown. *p < 0.001, **p = 0.029 (Bonferroni test). AR = atrial regurgitation; MR = mitral regurgitation.

to 1.04, p = 0.01) were predictive of long-term mortality. Chronic obstructive pulmonary disease and estimated glomerular filtration rate were associated with long-term mortality by univariate analysis; however, these predictors were no longer significant after adjustment for multivariable analysis.

Discussion

This study demonstrates that post-procedural AR after TAVI has a significant adverse effect on long-term outcome, as evidenced in both Edwards valve and CoreValve recipients, regardless of the type of bioprosthesis and LVEF.

Impact of post-procedural AR after TAVI on long-term mortality. In general, surgical aortic valve replacement is performed after resection of the native aortic valve; this ensures improved conformability of the aortic annulus with the sewing ring of the surgical valve. The TAVI technique is carried out by placing a stent-structured bioprosthesis and compressing the native aortic valve without resecting it; this may create a gap between the implanted bioprosthesis and the aortic valve when the native valve or annulus are calcified, thus causing post-procedural AR (4). As TAVI is a relatively recent technique, long-term follow-up data are not yet available, especially with respect to the durability of the bioprostheses. The need for treatment of post-procedural AR must be rigorously assessed before deciding whether post-dilation should be carried out after valve deployment.

Significant post-procedural AR (grade ≥2/4) after TAVI was recently identified as a predictor of late mortality in a study from the Italian registry using the CoreValve (5). Similar findings were reported in the German registry study (12), which showed that AR grade ≥2/4 post TAVI based on angiographic assessment was an independent predictor of 30-day mortality. In this registry, the CoreValve was also used in 82% of cases. These previous reports mainly concerned the cohort of CoreValve recipients; moreover, they did not contain any substantial data on the impact of AR grade 2 (compared with absence of AR) versus no AR on the severity of the outcome. In the study reported here, we clearly observed that not only AR grade 3 or 4, but also AR grade 2 had a significant impact on the long-term outcome (Fig. 1A, log-rank p < 0.01, group 1 vs. 2), regardless of the type of bioprosthesis used for TAVI (Figs. 2B and 2C). Furthermore, this finding was consistently recorded, not only in patients with reduced LVEF (Fig. 2E), but also in those with preserved LVEF (Fig. 2D). The same observation was briefly reported in the recently published 2-year follow-up results of the cohort A of the PARTNER (Placement of AoRTic TraNscathetER Valve) trial (13), and our data support these findings. We also analyzed the impact of "the change in the degree of AR between pre- and post-procedure" on mortality. Notably, the "change in the degree of AR" observed in the study reported here had a similar impact on mortality (Fig. 3, log-rank p = 0.03, Fig. 4, log-rank p < 0.01) as did the absolute value of post-procedural AR grade (Fig. 2, log-rank p < 0.01). Our results convey important clinical implications by demonstrating that not only post-procedural AR grade 3 or 4, but also AR grade 2, should be prevented by meticulous pre-procedural evaluation of the annulus size and treated by using post-dilation when indicated (14).

We recently reported that CT-guided valve selection allows better appreciation of the 3-dimensional structure of the aortic annulus and is potentially associated with a lower incidence of significant post-procedural AR (6). Routine implementation of this strategy may prevent the occurrence of this underestimated complication. Because post-dilation carries an inherent risk of annulus rupture and may promote accelerated bioprosthesis degeneration, excessive balloon oversizing should be avoided.

Interestingly, post-procedural MR increased in parallel with the degree of post-procedural AR (0.78 ± 0.73, 1.22 ± 0.80, and 1.89 ± 0.78, in groups 1, 2, and 3, respectively, Fig. 1) despite the absence of significant differences in pre-procedural MR. The degree of MR usually remains unchanged or even improves after TAVI, and aggravation of MR is a rare occurrence (15,16). In our study, improvement in MR was observed only in group 1; there was no improvement in group 2, and deterioration was

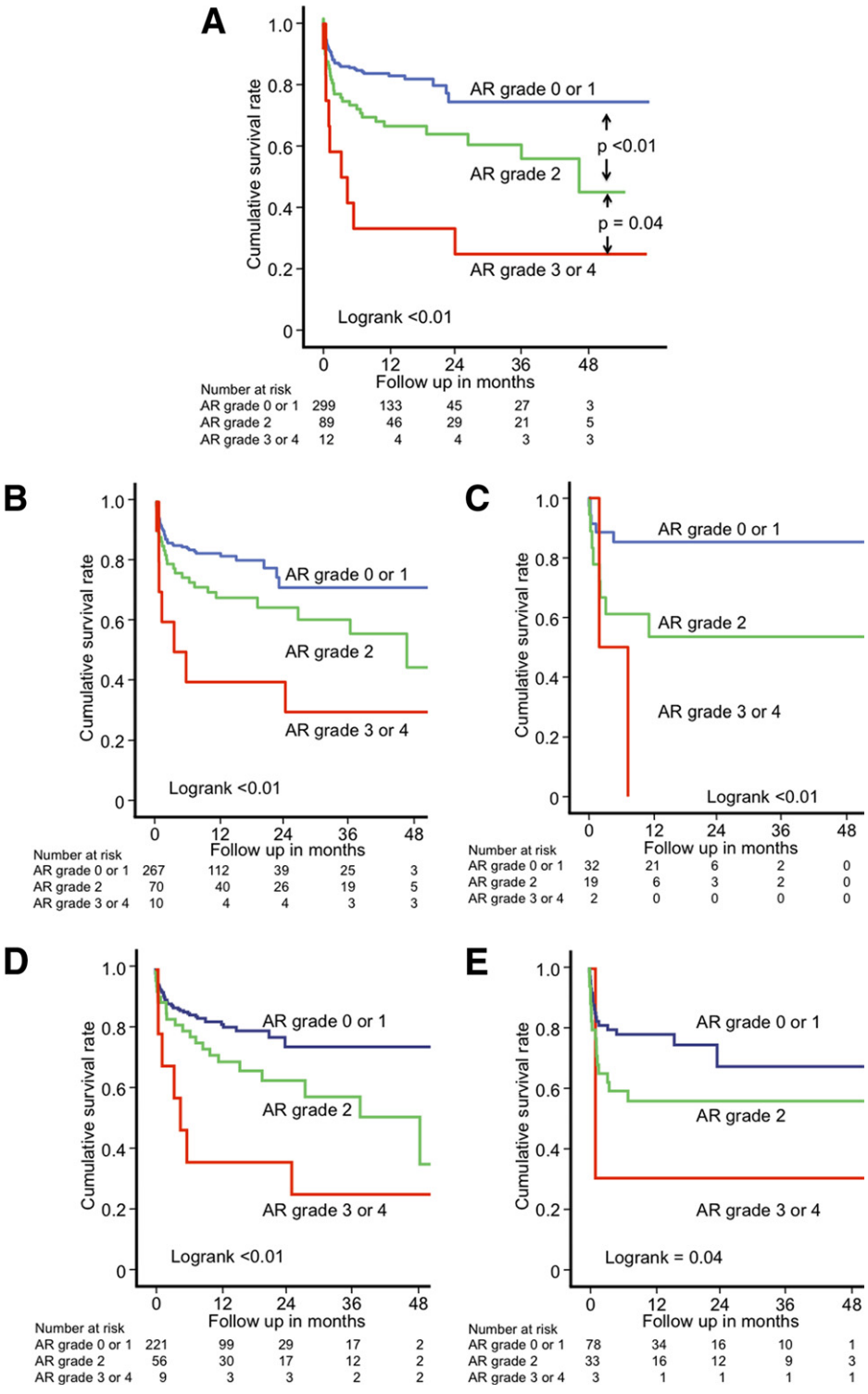

Figure 2. Survival Curves by Post-Procedural AR

Survival curves for post-procedural AR grade: 0 or 1 (group 1, **blue**), 2 (group 2, **green**), and 3 to 4 (group 3, **red**). Cumulative survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test. **(A)** Survival curves by post-procedural AR in the whole cohort. **(B)** Survival curves in the patients who received the Edwards valve. **(C)** Survival curves in the patients who received the CoreValve. **(D)** Survival curves in the patients who had LVEF ≥40%. **(E)** Survival curves in the patients who had LVEF <40%. AR = atrial regurgitation; LVEF = left ventricular ejection fraction.

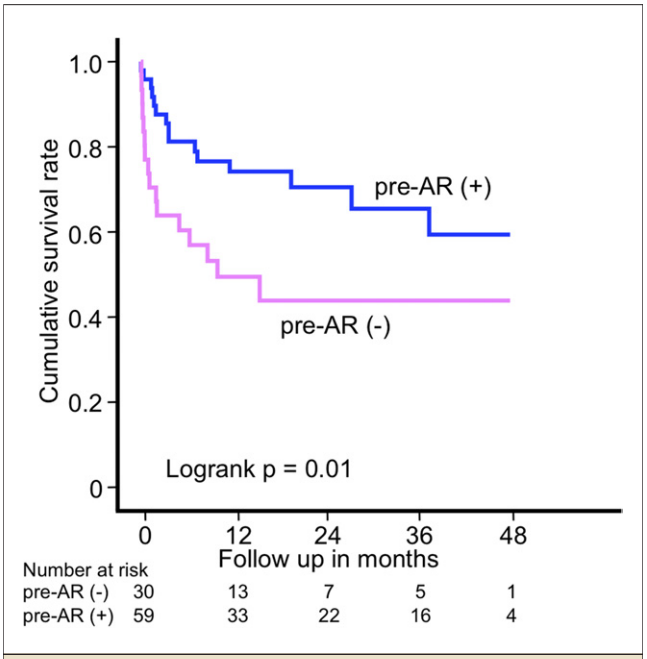

Figure 3. Survival Curves by the Pre-Procedural AR Grade in Group 2

Survival curves for the patients with no pre-procedural AR **(pink)** and those who had pre-procedural AR **(blue)**. Cumulative survival rates calculated by the Kaplan-Meier method and compared with the log-rank test. AR = atrial regurgitation.

observed in group 3. The mechanism underlying this finding is unclear. However, impaired hemodynamics and worsening heart failure resulting from post-procedural AR may aggravate MR and lead to higher mortality. The position of the bioprosthesis can also have an impact on AR and possibly on MR, which may be one possible explanation for our findings and remains to be explored.

Generally, AR grade 2 in itself does not seem to significantly impact clinical outcomes. However, the reason why post-procedural AR grade 2 influences the rate of mortality remains unclear. A hypertrophic left ventricle that has been exposed to long-term pressure overload may not be able to adapt abruptly to a diastolic overload, even in the presence of AR grade 2/4, especially when no pre-procedural AR has been observed (Fig. 3). The increase in post-procedural MR in parallel with AR (Fig. 1) may reflect the overload due to post-procedural AR.

In our cohort, the CoreValve was more frequently used in groups 2 and 3, where the incidence of significant AR was 39.6%. The reason for this has not been identified; however, the fact that the operators were less experienced in the use of the CoreValve (53 of 400 cases) may have had an impact on the higher incidence of significant AR. Indeed, whereas significant AR was observed in 33.5% of the first half of the Edwards valve recipients, it decreased to 12.6% in the remaining half of the patients, presumably due to the introduction of multidetector CT enabling accurate measurement. Furthermore, the CoreValve is generally used in patients with a larger annulus, including the upper limit of annulus size. This valve selection bias could have impacted these results.

Recently, the "AR index," which is derived from hemodynamic parameters, emerged as a new method for evaluating post-procedural AR and predicting 1-year mortality. This approach can prove useful in providing extra diagnostic information to complement the echocardiographic data (17).

Predictor of long-term mortality. In previously published reports (5–18,19), significant post-procedural AR was identified as 1 of the predictors of long-term mortality (5,20), as was acute kidney injury (18,19). Our results are in line with these findings.

As suggested in our recent report (10), male sex was also identified as a predictor in the current study. The CoreValve was used more frequently in groups 2 and 3 and the association between post-procedural AR and this bioprosthesis has also been reported previously (12). However, the type of bioprosthesis used for TAVI was not identified as a predictor of long-term mortality (Table 3).

Study limitations. Our study reports a retrospective single-center TAVI cohort of limited size. We opted to include recipients of both the Edwards valve and the CoreValve, as this mixed cohort reflected our real clinical experience. The quantification of paravalvular aortic regurgitation was sometimes difficult due to the confined nature of the jet(s) and the absence of an echo core laboratory; however, the assessment was achieved according to the guidelines by 2

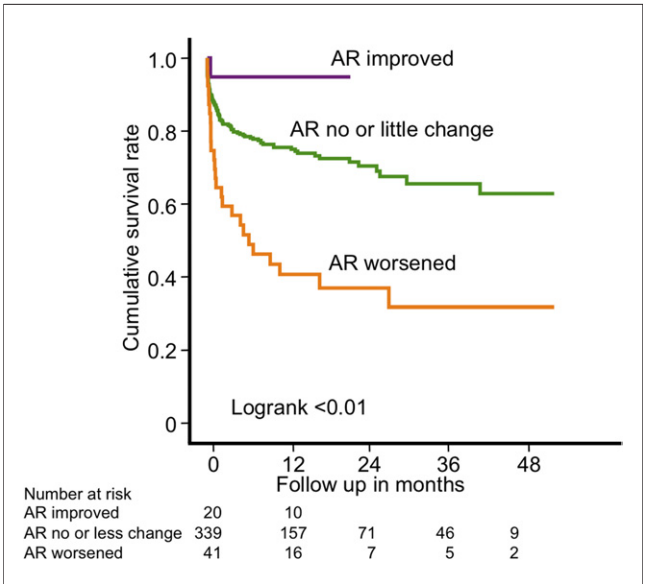

Figure 4. Survival Curves by the Increase in AR

Survival curves for the change of AR: improved **(purple)**, no or little change **(green)**, and worsened **(orange)**. Cumulative survival rates calculated by the Kaplan-Meier method and compared with the log-rank test. AR = atrial regurgitation.

Table 3. Predictors of Long-Term Mortality

	p Value	Univariate Hazard ratio	95% CI	p Value	Multivariable Hazard ratio	95% CI
Post-procedural aortic regurgitation ≥2/4	<0.01	1.75	1.20–2.54	<0.01	1.7	1.13–2.56
Conversion to open heart surgery	<0.01	6.58	3.18–13.62	<0.01	5.98	2.61–13.70
Major stroke	<0.01	4.37	1.91–9.98	0.01	4.51	1.90–10.71
Acute kidney injury	<0.01	2.65	1.61–4.35	0.01	2.19	1.21–3.95
Major vascular complication	<0.01	2.71	1.72–4.29	0.05	1.73	1.00–3.01
Transfusion ≥4 units	<0.01	3.66	2.29–5.83	0.01	2.21	1.17–4.17
Logistic EuroSCORE	<0.01	1.02	1.01–1.04	0.01	1.01	1.01–1.04
eGFR <60 ml/min.	<0.01	1.87	1.23–2.86	0.41		
COPD	0.05	1.41	0.99–2.03	0.48		
Male sex	0.07	1.36	0.95–1.94			
Previous CABG	0.12	1.45	0.93–2.25			
Left ventricular ejection fraction	0.32	1.21	0.83–1.78			
Age	0.32	1.02	0.99–1.05			
Type of bioprosthesis	0.59	0.87	0.53–1.44			

CI = confidence interval; other abbreviations as in Tables 1 and 2.

independent experienced echocardiographers. The mechanism of AR worsening was not analyzed in detail, because the focus of the study was the clinical impact of AR regardless of its precise cause. The occurrence and impact of aortic regurgitation over time during follow-up was not analyzed in this paper as this was not the aim of this study. Further studies of larger patient populations are required to confirm our results. Both Edwards Sapien and Sapien-XT valves were included, despite the differences in material (stainless steel for the former and cobalt-chromium for the latter).

Conclusions

Significant post-procedural AR after TAVI was identified as an independent predictor of long-term mortality. It was shown to have a significant adverse effect on long-term outcome regardless of the type of bioprosthesis used and LVEF. AR grade 2 was associated with deteriorated outcome compared with AR grade 0 or 1. Careful valve selection based on meticulous pre-procedural annulus sizing and post-dilation when required to avoid, not only grade 3 or 4, but also post-procedural AR grade 2, may contribute to improving the clinical outcome of TAVI patients.

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Key Words: aortic stenosis ■ mortality ■ paravalvular regurgitation ■ predictor ■ transcatheter aortic valve implantation.