JACC: CARDIOVASCULAR INTERVENTIONS VOL. 7, NO. 9, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2014.04.012

Clinical Impact of Aortic Regurgitation After Transcatheter Aortic Valve Replacement

Insights Into the Degree and Acuteness of Presentation

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ABSTRACT

OBJECTIVES The aim of this study was to determine the impact of the degree of residual aortic regurgitation (AR) and acuteness of presentation of AR after transcatheter aortic valve replacement (TAVR) on outcomes.

BACKGROUND The degree of residual AR after TAVR leading to excess mortality remains controversial, and little evidence exists on the impact of the acuteness of presentation of AR.

METHODS A total of 1,735 patients undergoing TAVR with balloon-expandable or self-expanding valves were included. The presence and degree of AR were evaluated by transthoracic echocardiography; acute AR was defined as an increase in AR severity of ≥1 degree compared with pre-procedural echocardiography.

RESULTS Residual AR was classified as mild in 761 patients (43.9%) and moderate to severe in 247 patients (14.2%). The presence of moderate to severe AR was an independent predictor of mortality at a mean follow-up of 21 ± 17 months compared with none to trace (adjusted hazard ratio [HR]: 1.81, 95% confidence interval [CI]: 1.32 to 2.48; $p < 0.001$) and mild AR (adjusted HR: 1.68, 95% CI: 1.27 to 2.24; $p < 0.001$) groups. There was no increased risk in patients with mild AR compared with those with none to trace AR ($p = 0.393$). In patients with moderate to severe AR, acute AR was observed in 161 patients (65%) and chronic AR in 86 patients (35%). Acute moderate to severe AR was independently associated with increased risk of mortality compared with none/trace/mild AR (adjusted HR: 2.37, 95% CI: 1.53 to 3.66; $p < 0.001$) and chronic moderate to severe AR (adjusted HR: 2.24, 95% CI: 1.17 to 4.30; $p = 0.015$). No differences in survival rate were observed between patients with chronic moderate to severe and none/trace/mild AR ($p > 0.50$).

CONCLUSIONS AR occurred very frequently after TAVR, but an increased risk of mortality at ~2-year follow-up was observed only in patients with acute moderate to severe AR. (J Am Coll Cardiol Intv 2014;7:1022–32)

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Manuscript received February 28, 2014; revised manuscript received April 9, 2014, accepted April 24, 2014.

Residual aortic regurgitation (AR) is considered to be one of the most important limitations of transcatheter aortic valve replacement (TAVR) with an incidence of mild or more than mild paravalvular leaks of >50% in most series, which markedly exceeds that observed after standard surgical aortic valve replacement (1–3). Several studies have shown that the presence of moderate to severe residual AR after TAVR is one of the strongest predictors of acute mortality and at mid-term follow-up (1–14). However, efforts to determine the clinical impact of mild residual AR have yielded inconsistent results (4,6,11,13–17), and whether mild AR after TAVR is associated with poorer outcomes remains controversial. Further clarification of this issue is of high clinical relevance, especially considering both the high incidence of mild AR after TAVR and the potentially deleterious effects and costs associated with additional measures for the treatment of paravalvular leaks in such cases (e.g., balloon post-dilation, implantation of a second valve, paravalvular leak closure) (18–20).

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The early negative effect of residual AR on TAVR candidates contrasts with the clinical evidence on the impact of moderate or even severe AR in the overall population, which commonly progress slowly, with a long latency period before the appearance of symptoms or complications (21,22). It was recently suggested that the acuteness of residual AR after TAVR might have an impact on late mortality. In particular, the worsening of ≥2 degrees in AR after TAVR was found to be associated with increased mortality (4). However, the degree of AR in this group of patients was not detailed, no adjustment for confounding factors was performed, and whether the impact of the acuteness of presentation of AR was independent of the occurrence of moderate to severe AR was not determined. Moreover, few data exist on the impact of residual AR on cardiovascular outcomes, including cardiac (rather than global) mortality and echocardiographic parameters (6,17,23). The objectives of this study, therefore, were the following: 1) to evaluate the impact of the severity and acuteness of AR after TAVR on clinical outcomes (global and cardiovascular) and 2) to assess the impact of residual AR on left ventricular ejection fraction (LVEF) and mitral regurgitation (MR) changes as evaluated by echocardiography.

METHODS

STUDY POPULATION. A total of 1,783 consecutive patients undergoing TAVR with balloon-expandable valves (982 patients) and self-expanding valves (753 patients) at 8 centers were evaluated. Forty-eight patients were excluded because of the following reasons: unsuccessful procedure without valve implantation in 30 patients, death during the first 24 h after TAVR before an echocardiogram was performed in 17 patients, and concomitant transcatheter mitral valve-in-valve implantation in 1 patient. Therefore, the final study population consisted of 1,735 patients. Details about the number of patients, and type of valves in each center are provided in Online Figure 1. Eligibility for TAVR, valve type, and access

ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation
CI = confidence interval
HR = hazard ratio
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
TAVR = transcatheter aortic valve replacement
VARC-2 = Valve Academic Research Consortium 2

TABLE 1 Baseline Clinical Characteristics and Echocardiographic and Procedural Findings According to the Severity of AR After TAVR

	All (n = 1,735)	None to Trace AR (n = 727)	Mild AR (n = 761)	Moderate to Severe AR (n = 247)	p Value
Clinical characteristics					
Age, yrs	81 ± 7	80 ± 7	81 ± 7*	80 ± 8	0.002
Male	848 (48.9)	306 (42.1)	402 (52.8)*	140 (56.7)†	<0.001
Body mass index, kg/m^2	27 ± 5	27 ± 5	27 ± 5*	26 ± 5†	<0.001
Hypertension	1,417 (81.7)	634 (87.3)	595 (78.2)*	188 (76.1)†	<0.001
Diabetes	553 (31.9)	252 (34.7)	238 (31.3)	63 (25.6)†	0.024
NYHA functional class ≥3	1,403 (80.9)	585 (80.5)	620 (81.5)	198 (80.2)	0.833
Chronic atrial fibrillation	403 (23.2)	140 (19.3)	208 (27.3)*	55 (22.3)	0.001
CABG	413 (23.8)	181 (24.9)	182 (23.9)	50 (20.2)	0.337
COPD	548 (31.6)	243 (33.4)	220 (29.2)	83 (33.6)	0.165
eGFR <60 ml/min	955 (55.0)	401 (55.2)	410 (53.9)	144 (58.3)	0.561
STS-PROM score, %	7.7 ± 5.2	7.3 ± 5.1	8.1 ± 5.3*	7.6 ± 5.0	0.003
Logistic EuroSCORE, %	20.8 ± 13.9	20.3 ± 13.7	21.5 ± 14.1	20.5 ± 13.9	0.119
Echocardiographic findings					
LVEF <40%	327 (18.8)	119 (16.4)	146 (19.2)	62 (25.1)†	0.011
Aortic mean gradient, mm Hg	46 ± 17	45 ± 16	47 ± 16*	49 ± 18†	<0.001
Aortic valvular area, cm^2	0.65 ± 0.20	0.67 ± 0.21	0.63 ± 0.18*	0.64 ± 0.18	0.018
Systolic pulmonary artery pressure >55 mm Hg	268 (15.4)	98 (13.5)	125 (16.4)	45 (18.1)	0.116
Procedural findings					
Approach					<0.001
Transfemoral/subclavian	1,282 (73.9)	463 (63.7)	607 (79.8)*	212 (85.8)†‡	
Transapical/transaortic	453 (26.1)	264 (36.3)	154 (20.2)	35 (14.2)	
Prosthesis type					<0.001
Self-expanding valve	753 (43.4)	281 (38.7)	325 (42.7)	147 (59.5)†‡	
Balloon-expandable valve	982 (56.6)	446 (61.3)	436 (57.3)	100 (40.5)	
Prosthesis size					<0.001
20–23	452 (26.1)	225 (30.9)	182 (23.9)	45 (18.2)	
26	870 (50.1)	352 (48.4)	402 (52.8)	116 (47.0)†‡	
29–31	413 (23.8)	150 (20.6)	177 (23.3)*	86 (34.8)†‡	

Values are mean ± SD or n (%). *p < 0.05 versus none/trace. †p < 0.05 versus none/trivial. ‡p < 0.05 versus mild.

AR = aortic regurgitation; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS-PROM = Society of Thoracic Surgeons predicted risk of mortality; TAVR = transcatheter aortic valve replacement.

TABLE 2 30-Day Clinical Outcomes According to the Severity of AR After TAVR

30-Day Outcomes	All (n = 1,735)	None to Trace AR (n = 727)	Mild AR (n = 761)	Moderate to Severe AR (n = 247)	p Value
Permanent pacemaker implantation	256 (14.8)	96 (13.2)	114 (15.0)	46 (18.6)	0.120
Myocardial infarction	17 (1.0)	7 (1.0)	9 (1.2)	1 (0.4)	0.539
Major/life-threatening bleeding	261 (15.0)	94 (12.9)	123 (16.2)	44 (17.8)	0.091
Major vascular complications	130 (7.5)	61 (8.4)	55 (7.3)	14 (5.7)	0.361
Acute kidney disease	322 (18.6)	122 (16.8)	145 (19.5)	55 (22.3)	0.087
Stroke	59 (3.4)	22 (3.0)	26 (3.4)	11 (4.5)	0.539
Death	95 (5.5)	31 (4.3)	35 (4.6)	29 (11.7)*†	<0.001

Values are n (%). *Versus none/trace: odds ratio: 2.99, 95% confidence interval: 1.76 to 5.07; p < 0.001. †Versus mild: odds ratio: 2.76, 95% confidence interval: 1.65 to 4.62; p < 0.001.
Abbreviations as in Table 1.

route were determined at each center by a local heart team composed of interventional cardiologists and cardiac surgeons. Clinical, procedural, and echocardiographic data were prospectively gathered into a TAVR database at each participating center. Outcomes were defined according to the Valve Academic Research Consortium 2 (VARC-2) criteria (24).

Clinical follow-up was carried out in clinical visits and/or through phone contact at 1 month, 6 to 12 months after TAVR, and yearly thereafter in all participating centers. No patient was lost during follow-up. Outcomes were defined according to the VARC-2 criteria.

ECHOCARDIOGRAPHIC ASSESSMENT. Transthoracic echocardiography examinations were systematically performed at baseline, after the procedure, and at hospital discharge. Echocardiographic data at 6-month to 12-month follow-up were available for 1,076 patients (71% of patients alive). Only transthoracic echocardiography examinations were considered for the definition of AR. Echocardiograms were analyzed by expert echocardiographers at each center. The presence and degree of AR were evaluated according to the VARC-2 criteria, and patients were classified into 3 groups according to the severity of residual AR: none to trace, mild, and moderate to severe. In a further analysis, moderate to severe AR was also subclassified as acute if there was ≥1 degree of increase in AR compared with baseline and as chronic when no changes or decrease in AR occurred compared with baseline assessment. The LVEF was evaluated in all patients using the Simpson biplane methods. The presence of MR was also assessed in all cases, and the severity was classified as none to trace, mild, moderate, and severe according to the recommendations of the American Society of Echocardiography (25).

TABLE 3 Impact of the Severity of AR After TAVR on Cumulative Mortality

	None to Trace AR (n = 727)	Mild AR (n = 761)	Moderate to Severe AR (n = 247)	p Value: Mild vs. None to Trace	p Value: Moderate to Severe vs. None to Trace	p Value: Moderate to Severe vs. Mild
Overall mortality						
No. of patients	153 (21.0)	212 (27.9)	89 (36.0)			
Moderate to severe and mild vs. none to trace AR						
Univariate HR	1.00 (ref.)	1.11 (0.90–1.36)	1.60 (1.24–2.08)	0.350	<0.001	
Multivariate HR*	1.00 (ref.)	1.07 (0.84–1.37)	1.81 (1.32–2.48)	0.567	<0.001	
Moderate to severe vs. mild AR						
Univariate HR		1.00 (ref.)	1.45 (1.13–1.86)			0.003
Multivariate HR*		1.00 (ref.)	1.68 (1.27–2.24)			<0.001
Cardiovascular mortality						
No. of patients	99 (13.6)	138 (18.1)	61 (24.7)			
Moderate-severe and mild vs. none-trace AR						
Univariate HR	1.00 (ref.)	1.13 (0.87–1.46)	1.72 (1.25–2.37)	0.371	0.001	
Multivariate HR*	1.00 (ref.)	1.11 (0.82–1.49)	1.68 (1.13–2.48)	0.514	0.010	
Moderate-severe vs. mild AR						
Univariate HR		1.00 (ref.)	1.53 (1.13–2.07)			0.006
Multivariate HR*		1.00 (ref.)	1.52 (1.06–2.18)			0.024

Values are n (%) or hazard ratio (95% confidence interval). *Adjusted for differences in baseline characteristics, procedural findings, and 30 day-outcome: age, male sex, body mass index, hypertension, diabetes, chronic atrial fibrillation, STS-PROM, left ventricular ejection fraction <40%, transvalvular aortic gradient, aortic valve area, transapical/transaortic approach, the use of balloon-expandable valves, prosthesis size, 30-day life-threatening bleeding, and 30-day acute kidney injury.
ref. = reference; other abbreviations as in Table 1.

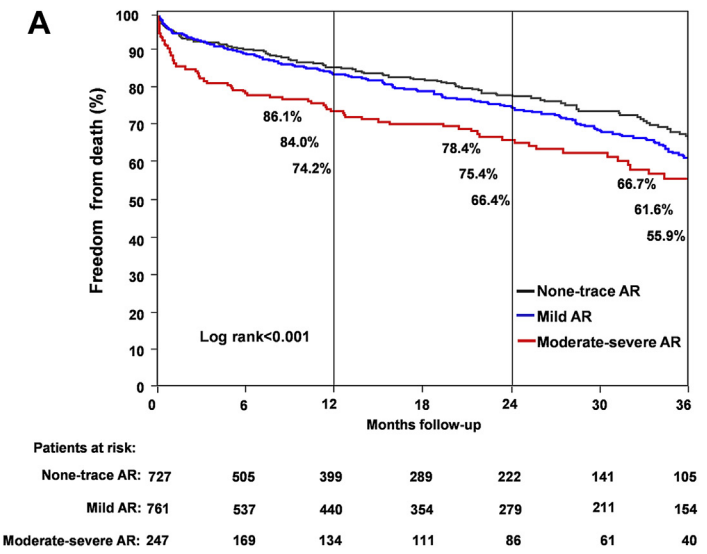
STATISTICAL ANALYSIS. Categorical variables are presented as frequencies and continuous variables as mean ± SD. Transvalvular mean gradient, body mass index, aortic valve area, STS-PROM (Society of Thoracic Surgeons predicted risk of mortality), and logistic EuroSCORE were skewed to the right and thus were analyzed using a logarithmic transformation. Comparisons of continuous variables were performed using analysis of variance. The Fisher exact test was used to compare qualitative variables. The Tukey test for multiple comparisons was used if statistical significance was achieved. Logistic regression was used to determine the independent predictors of 30-day mortality. Cox regression models were used to analyze the impact of AR on late mortality. Log-transformed variables were entered into the models after logarithmic transformation. Variables (baseline, procedural, or post-procedural) with a p value < 0.10 on univariate analyses were included in multivariate analyses. The proportional hazards assumption was evaluated for all Cox models. Cumulative survival rates were calculated by the Kaplan-Meier method and compared with the log-rank test. A repeated-measures model with interactions was used to assess the changes in LVEF, MR, AR, mean transvalvular gradient, and aortic valve area over time between groups. Further comparisons were performed using the Bonferroni adjustment for multiple testing. A 2-sided p value <0.05 was considered significant. All statistical analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

The main baseline and procedural characteristics of the study population are shown in Table 1. A total of 1,008 patients (58.1%) had more than none to trace AR after TAVR and residual AR was classified as mild in 761 patients (43.9%) and moderate to severe in 247 patients (14.2%).

IMPACT OF THE SEVERITY OF AR ON MORTALITY. Thirty-day outcomes of the study population according to the severity of AR after TAVR are shown in Table 2. No differences were observed in the rate of periprocedural complications other than death between groups (p > 0.05 for all). The presence of moderate to severe AR was associated with increased 30-day mortality compared with none to trace and mild AR groups (odds ratio [OR]: 2.99; 95% confidence interval [CI]: 1.76 to 5.07; p < 0.001 and OR: 2.76, 95% CI: 1.65 to 4.62; p < 0.001, respectively), and these differences persisted after adjusting for baseline and procedural differences (adjusted OR: 2.69; 95% CI: 1.34 to 5.38; p = 0.005 and adjusted OR: 2.41, 95% CI: 1.27 to 4.57; p = 0.007 for comparisons with none to trace and mild AR groups, respectively). No increased risk of 30-day mortality was observed in patients with mild AR compared with none to trace AR (OR: 0.91, 95% CI: 0.73 to 1.12; p = 0.350).

At a mean follow-up of 21 ± 17 months, 454 (26.2%) patients had died: 153 (21.0%) patients in the none to



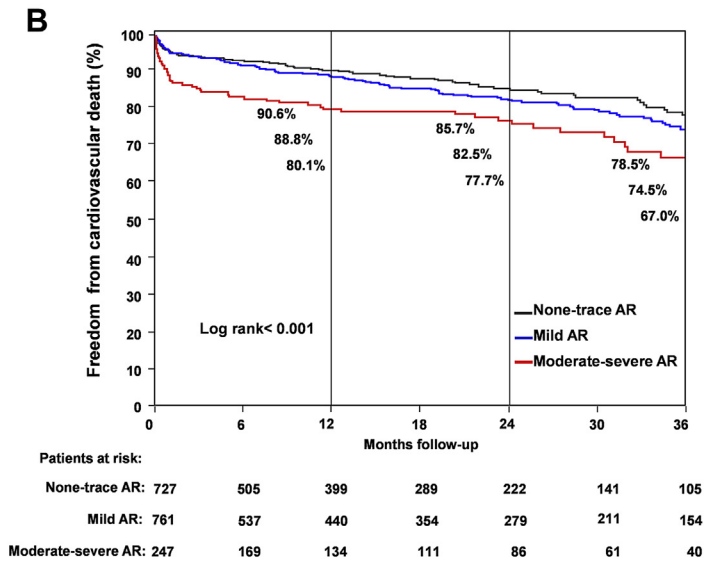


FIGURE 1 Survival Curves According to the Degree of AR After TAVR

Kaplan-Meier curves at 3-year follow-up showing the percentage of patients free of death **(A)** and cardiovascular death **(B)** according to the degree of aortic regurgitation (AR) after transcatheter aortic valve replacement (TAVR).

TABLE 4 Baseline Characteristics and Procedural Findings According to the Occurrence of None to Mild, Acute or Chronic Moderate to Severe AR

	None to Trace to Mild AR (n = 1,488)	Chronic Moderate to Severe AR (n = 86)	Acute Moderate to Severe AR (n = 161)	p Value
Clinical characteristics				
Age, yrs	81 ± 7	80 ± 9	80 ± 8	0.677
Male	708 (47.6)	49 (57.0)	91 (56.5)†	0.030
Body mass index, kg/m^2	27 ± 5	25 ± 5*	26 ± 5	0.002
Hypertension	1,231 (82.7)	64 (74.4)*	122 (75.8)†	0.018
Diabetes	490 (32.9)	13 (15.1)*	50 (31.1)‡	0.001
NYHA functional class ≥3	1,205 (81.0)	75 (87.2)	123 (76.4)	0.122
Chronic atrial fibrillation	348 (23.4)	21 (24.4)	34 (21.1)	0.788
CABG	363 (24.4)	14 (16.3)	36 (22.4)	0.211
COPD	465 (31.3)	30 (34.9)	53 (32.9)	0.704
eGFR <60 ml/min	811 (54.5)	54 (62.8)	90 (55.9)	0.324
STS-PROM score, %	7.7 ± 5.2	8.3 ± 5.4	7.2 ± 4.8	0.110
Logistic EuroSCORE, %	20.9 ± 13.9	22.7 ± 13.7	19.2 ± 13.9	0.065
Echocardiographic characteristics				
LVEF <40%	265 (17.8)	18 (20.9)	44 (27.3)†	0.014
Aortic mean gradient, mm Hg	46 ± 16	50 ± 18	48 ± 17	0.043
Aortic valvular area, cm^2	0.65 ± 0.20	0.64 ± 0.21	0.64 ± 0.16	0.923
Systolic pulmonary artery pressure >55 mm Hg	223 (15.0)	20 (23.3)	25 (15.5)	0.206
Procedural findings				
Approach				<0.001
Transfemoral/subclavian	1,070 (71.9)	80 (93.0)*	132 (82.0)†‡	
Transapical/transaortic	418 (28.1)	6 (7.0)	29 (18.0)	
Prosthesis type				<0.001
Self-expanding valve	606 (40.7)	64 (74.4)*	83 (51.6)†‡	
Balloon-expandable valve	882 (59.3)	22 (25.6)	78 (48.4)	
Prosthesis size				<0.001
20–23	407 (27.4)	10 (11.6)	35 (21.7)	
25–26	754 (50.7)	38 (44.2)*	78 (48.4)	
29–31	327 (22.0)	38 (44.2)*	48 (29.8)†‡	

Values are mean ± SD or n (%). *p < 0.05 versus none/trace. †p < 0.05 versus none/trivial. ‡p < 0.05 versus mild.
Abbreviations as in Table 1

trace AR group, 212 patients (27.9%) in the mild AR group, and 89 patients (36.0%) in the moderate to severe AR group. The presence of moderate to severe AR was associated with increased overall mortality compared with patients with none to trace AR (hazard ratio [HR]: 1.60, 95% CI: 1.24 to 2.08; p < 0.001) and mild AR (HR: 1.45, 95% CI: 1.13 to 1.86; p < 0.001), and these differences persisted after adjusting for baseline and procedural differences between groups (adjusted HR: 1.81; 95% CI: 1.32 to 2.48; p < 0.001 and adjusted HR: 1.68, 95% CI: 1.27 to 2.24; p < 0.001 for comparisons with none to trace and mild AR groups, respectively). Also, moderate to severe AR was independently associated with an increased risk of cardiovascular mortality compared with none to trace and mild AR groups (adjusted HR: 1.68, 95% CI: 1.13 to 2.48; p = 0.010 and adjusted HR: 1.52, 95% CI: 1.06 to 2.18; p = 0.024, respectively). No increased overall or cardiovascular mortality was observed in patients with mild AR in both univariate and multivariate analyses (p > 0.30 for all comparisons) (Table 3). The Kaplan-Meier curves for overall and cardiovascular mortality at 3-year follow-up according to the degree of AR are shown in Figure 1.

IMPACT OF ACUTE (VS. CHRONIC) AR. To further evaluate the impact of the acuteness of presentation of AR in patients with moderate to severe AR after TAVR, patients were reclassified into 3 groups: none/trace/mild AR (n = 1,448 [83%]), chronic moderate to severe AR (n = 86 [5.0%]), and acute moderate to severe AR (n = 161 [9.3%]). Baseline clinical and echocardiographic characteristics and procedural findings according to these groups are shown in Table 4.

The rates of periprocedural complications other than death were similar between groups (p > 0.10 for all) (Table 5). Patients with acute moderate to severe AR showed an increased risk of 30-day mortality compared with the none/trace/mild AR group (OR: 3.59, 95% CI: 2.17 to 5.95; p < 0.001), and a trend toward an increased mortality when comparing to chronic moderate to severe AR (OR: 2.22, 95% CI: 0.87 to 5.69; p = 0.096). On multivariate analysis, acute moderate to severe AR strongly predicted 30-day mortality compared with none/trace/mild (adjusted OR: 4.81, 95% CI: 2.07 to 11.18; p < 0.001). No significant differences were observed compared with chronic moderate to severe AR group (p = 0.081). There were no differences in 30-day mortality between chronic moderate to severe and none/trace/mild AR groups (OR: 1.62, 95% CI: 0.68 to 3.84; p = 0.227).

At last follow-up, 365 patients (24.5%) with none to mild AR, 23 patients (26.7) with chronic moderate to severe AR, and 66 patients (41%) with acute moderate to severe AR had died. The occurrence of acute moderate to severe AR was an independent predictor of overall mortality compared with none/trace/mild AR (adjusted HR: 2.37; 95% CI: 1.53 to 3.66; p < 0.001) and chronic moderate to severe AR (adjusted HR: 2.24, 95% CI: 1.17 to 4.30; p = 0.015). Also, patients with acute moderate to severe AR group exhibited an increased cardiovascular mortality compared with none/trace/mild AR (adjusted HR: 2.52, 95% CI: 1.48 to 4.32; p < 0.001) and chronic moderate to severe AR (adjusted HR: 2.32, 95% CI: 1.03 to 5.20; p = 0.041) (Table 6). Differences between chronic and acute moderate to severe AR groups persisted after further adjustment including 30-day vascular complication,

stroke, and acute kidney injury on multivariate analysis: adjusted HR: 2.15; 95% CI: 1.11 to 4.16; p = 0.023 for overall mortality and adjusted HR: 2.27, 95% CI: 1.01 to 5.11; p = 0.048 for cardiovascular mortality.

Survival curves at 3-year follow-up showing survival free of overall mortality and cardiovascular mortality according to the occurrence of none/trace/mild AR, chronic, and acute moderate to severe AR after TAVR are shown in Figure 2.

ECHOCARDIOGRAPHIC FINDINGS. Changes in aortic valve area and mean gradient according to the occurrence of none to trace, mild, and moderate to severe AR (chronic and acute) are shown in Figure 3. Small variations in aortic valve area at discharge and follow-up were observed between groups (p = 0.020 and 0.028, respectively), with no differences in transvalvular mean gradient (p > 0.50 for all). Changes in LVEF over time were similar between groups (p = 0.129), and no differences were observed in LVEF at discharge and at follow-up between groups (p > 0.2 for all) (Figure 4). Patients with acute moderate to severe AR showed a poorer evolution of MR over time compared with both patients with none/trace/mild (p = 0.042) and chronic moderate to severe AR (p = 0.008), whereas no differences were encountered in the evolution of MR between chronic moderate to severe and none/trace/mild AR groups (p = 0.170) (Figure 5). Although patients with none/trace/mild AR and chronic moderate to severe AR showed an improvement in MR severity over time (p < 0.001 for both), no improvement in the presence or severity of MR was observed in patients with acute moderate to severe AR (p = 0.951) (Figure 5). Differences in MR changes between groups persisted after

TABLE 5 30-Day Outcomes According to None to Mild, Chronic Moderate to Severe, and Acute Moderate to Severe AR Groups

	None to Trace to Mild AR (n = 1,488)	Chronic Moderate to Severe AR (n = 86)	Acute Moderate to Severe AR (n = 161)	p Value
30-day outcomes				
Permanent pacemaker implantation	210 (14.1)	18 (20.9)	28 (17.4)	0.134
Myocardial infarction	16 (1.1)	0	1 (0.6)	0.999
Major/life-threatening bleeding	217 (14.6)	14 (16.3)	30 (18.6)	0.354
Major vascular complications	116 (7.8)	3 (3.5)	11 (6.8)	0.349
Acute kidney disease	267 (17.9)	17 (19.8)	38 (23.6)	0.199
Stroke	48 (3.2)	2 (2.3)	9 (5.6)	0.279
Death	66 (4.4)	6 (7.0)	23 (14.3)*†	<0.001

Values are n (%). *Versus none/trace/mild: odds ratio: 3.59, 95% confidence interval: 2.17 to 5.95; p < 0.001. †Versus chronic moderate to severe AR: odds ratio: 2.22, 95% confidence interval: 0.87 to 5.69; p = 0.096.

TABLE 6 Impact of the Occurrence of None to Mild, Acute or Chronic Moderate to Severe AR After TAVR on Cumulative Mortality

	None to Trace to Mild AR (n = 727)	Chronic Moderate to Severe AR (n = 86)	Acute Moderate to Severe AR (n = 161)	p Value		
				Chronic Moderate to Severe vs. None/Trace/Mild	Acute Moderate to Severe vs. None/Trace/Mild	Acute vs. Chronic Moderate to Severe
Overall mortality						
No. of patients	365 (24.5)	23 (26.7)	66 (41.0)			
Acute and chronic moderate to severe vs. none to mild AR						
Univariate HR	1.00 (ref.)	0.94 (0.61–1.43)	1.93 (1.49–2.53)	0.755	<0.001	
Multivariate HR*	1.00 (ref.)	1.06 (0.60–1.86)	2.37 (1.53–3.66)	0.848	<0.001	
Acute vs. chronic moderate to severe AR						
Univariate HR		1.00 (ref.)	2.07 (1.29–3.33)			0.003
Multivariate HR*		1.00 (ref.)	2.24 (1.17–4.30)			0.015
Cardiovascular mortality						
No. of patients	237 (15.9)	16 (18.6)	45 (28.0)			
Acute and chronic moderate to severe vs. none-mild AR						
Univariate HR	1.00 (ref.)	1.03 (0.62–1.71)	2.02 (1.46–2.77)	0.917	<0.001	
Multivariate HR*	1.00 (ref.)	1.09 (0.54–2.21)	2.52 (1.48–4.32)	0.815	0.001	
Acute vs. chronic moderate to severe AR						
Univariate HR		1.00 (ref.)	1.96 (1.11–3.47)			0.021
Multivariate HR*		1.00 (ref.)	2.32 (1.03–5.20)			0.041

Values are n (%) or hazard ratio (95% confidence interval). *Adjusted for differences in baseline characteristics, procedural findings, and 30 day-outcome: male sex, body mass index, hypertension, diabetes, logistic EuroSCORE, left ventricular ejection fraction <40%, transvalvular aortic gradient, transapical/transaortic approach, the use of balloon-expandable valves, and prosthesis size.

Abbreviations as in Tables 1 and 3.

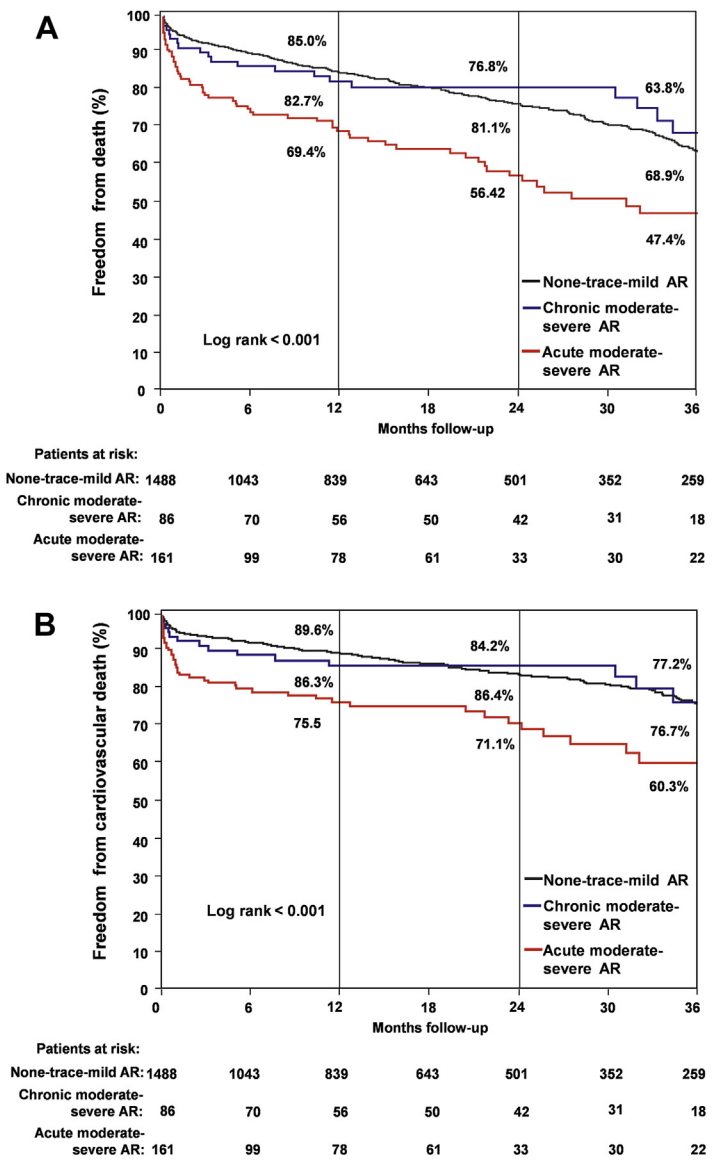


FIGURE 2 Survival Curves According to the Degree and Acuteness of Presentation of Post-Procedural AR

Kaplan-Meier curves at 3-year follow-up showing survival free of overall death **(A)** and cardiovascular death **(B)** according to the occurrence of post-procedural none/trace/mild, chronic, and acute moderate to severe aortic regurgitation (AR).

adjusting for differences in baseline LVEF and mean gradient (p = 0.034).

No changes were observed in the severity of AR from discharge to 6-month to 12-month follow-up (improvement in AR was observed in 16% of patients, and worsening in 18%, p=0.999) (Figure 6) and the evolution of AR was similar between patients with balloon-expandable and self-expanding valves (p = 0.387). The degree of AR was greater in the self-expanding valve group compared with the balloon-expandable valve group at all points of time (p ≤ 0.002 for all) (Figure 6).

DISCUSSION

As many as ~80% of patients undergoing TAVR show some degree of paravalvular leak, classified as mild in most of cases (2,3,12) and moderate to severe in ~12% of patients (14), similar to the proportion observed in this study. Although few data exist on the impact of mild AR after TAVR (4,13,14,17), some studies have suggested an increased risk of mortality associated with mild paravalvular leaks (4,13,14). Nonetheless, this finding was based on the results of unadjusted analyses, and it was not confirmed after adjustments for confounding variables (4,13,14). The present study showed that the survival in patients mild AR was similar to that observed in patients with none to trace AR, even despite a higher STS-PROM score in the mild AR group. This finding is consistent with most studies on surgical aortic valve replacement including the PARTNER I (Placement of Aortic Transcatheter Valve) trial (1,26-28). Also, consistent with these results, Yared et al. (17) did not find increased mortality in patients with mild AR after TAVR, and a substudy of the Canadian TAVR experience showed that the presence of mild AR was not associated with any negative impact on left ventricular function parameters up to 3-year follow-up (29).

Strong evidence exists on the negative impact of residual moderate to severe AR on survival after TAVR (1,5-11), and, in fact, it is defined as device failure according to the VARC-2 (24). Likewise, the presence of moderate to severe AR after TAVR was an independent predictor of overall and cardiovascular mortality compared with both the none to trace and mild AR groups in this study. Importantly, the negative impact of moderate to severe AR was observed periprocedurally with a 3-fold increase in the risk of 30-day mortality and persisted over time with a 1.5-fold increased risk of overall and cardiovascular mortality at ~2-year follow-up, confirming the results of previous smaller studies evaluating the risk of cardiovascular mortality associated with residual AR (6,23).

Hayashida et al. (4) reported that a worsening of ≥2 degrees in AR after TAVR was associated with a poorer survival at 1-year follow-up. However, the rate of moderate to severe AR in this group was not reported, the model was not adjusted for potential confounding factors, and no conclusion could be drawn as to whether the impact of AR worsening was independent of the presence of moderate to severe

AR. In an step further, we found that any worsening of the severity of AR (even by 1 degree) relative to baseline with a final degree of moderate to severe AR was a strong independent predictor of mortality in these patients. Of note, no differences in survival at 2-year follow-up were observed between patients with chronic moderate to severe AR (no significant changes in AR severity between baseline and after TAVR) and those with none to mild AR after TAVR, strongly suggesting that the acuteness of AR presentation plays a major role in the deleterious effects of moderate to severe AR after TAVR. Any degree of AR has been reported in as many as ~86% of patients with aortic stenosis, being moderate or greater in as many as 45% (30), and the presence of AR at baseline showed a protective effect in patients undergoing TAVR because of severe aortic stenosis in the FRANCE2 registry (31). However, this was not confirmed in the PARTNER trial (1), perhaps due to the fact that moderate to severe AR at baseline was an exclusion criterion in that trial.

It is well-known that acute AR is associated with a poor prognosis in the overall population (32–36), unlike that observed for chronic AR. Differences in clinical impact between these 2 entities may be explained by the presence of compensatory mechanisms in chronic AR, which are lacking in acute AR, finally leading to a rapid increase in end-diastolic pressure relative to regurgitant volume and a low forward stroke volume. Sinning et al. (11) reported that the ratio of the gradient between diastolic blood pressure and left ventricular end-diastolic pressure to systolic blood pressure (AR index) is a strong predictor of increased mortality in TAVR candidates, even after adjusting for the severity of residual AR, and this has been confirmed by other studies (23). We speculate that an AR index <0.25 might refer to patients with acute moderate to severe AR rather than to all patients with moderate to severe AR, and this could explain its superior impact on AR severity assessment. No assessment of the AR index was available in our study, and the correlation between AR acuteness and index will have to be evaluated in future studies.

The rapid increase in end-diastolic pressures in acute AR usually leads to a worsening in MR to lower diastolic pressures. Accordingly, the degree of MR did not improve in patients with acute moderate to severe AR after TAVR and tended to worsen despite the relief of the left ventricular obstruction, whereas MR severity significantly improved over time in all other TAVR groups. Of note, patients with chronic AR showed a reduction in MR over time, suggesting a decrease in end-diastolic pressures despite the persistence of moderate to severe AR. This interplay between MR and residual AR in patients undergoing TAVR has been previously suggested (4) and also has been reported for surgical prosthetic heart valves (37,38). Nonetheless, the clinical relevance of differences in MR changes over time remains to be determined.

In accordance with previous studies (17,29), no impact of residual AR was observed on LVEF changes over periods of time as long as 6 to 12 months of follow-up. Several factors might have contributed to

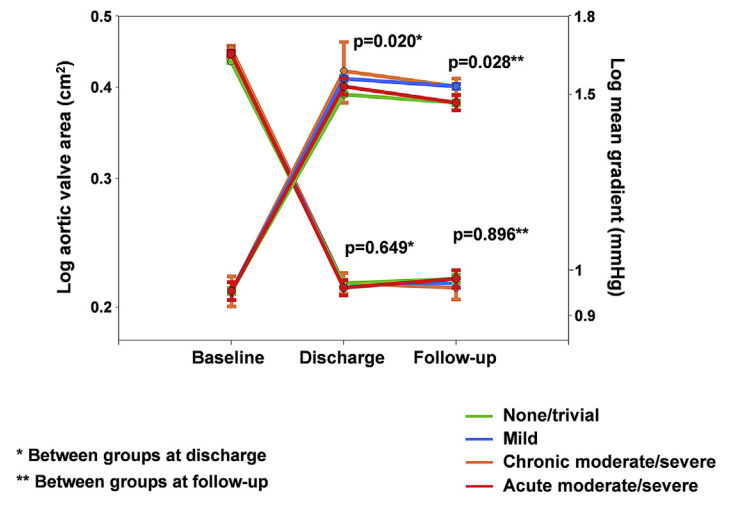


FIGURE 3 Changes in Valve Hemodynamics Over Time

Changes in transaortic mean gradients and aortic valve area according to the occurrence of none to trace, mild, chronic, and acute moderate to severe aortic regurgitation over time.

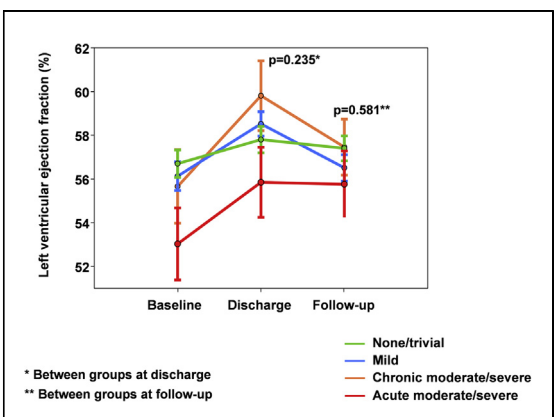


FIGURE 4 Changes in Left Ventricular Ejection Fraction Over Time According to Study Groups

Of note, only patients with evaluation of the left ventricular ejection fraction at the 3 points of time were included (N = 1,069).

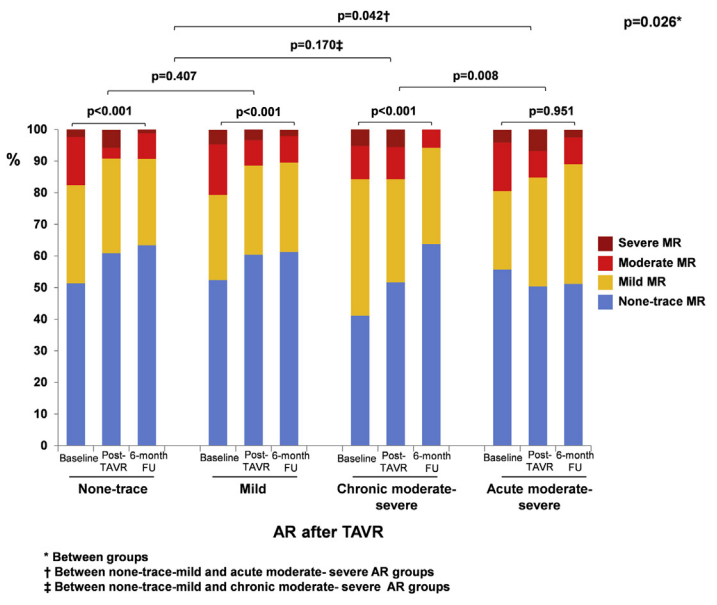


FIGURE 5 Changes in MR Over Time

Changes according to the occurrence of none to trace, mild, chronic, and acute moderate to severe aortic regurgitation (AR). Of note, only patients with evaluation of mitral regurgitation (MR) at the 3 points of time were included (N = 1,020). FU = follow-up; TAVR = transcatheter aortic valve replacement.

this finding. Consistent with previous studies (1), patients with moderate to severe AR had a lower LVEF and a higher mean transaortic gradient at baseline. It has been shown that a lower LVEF before TAVR is one of the strongest predictors of improvement in LVEF over time (39) and, therefore, greater improvement in LVEF after the relief of valve obstruction may compensate for any potential negative impact of residual AR in these patients. Also, moderate to severe AR was associated with an increased early mortality. Hence, those patients with moderate to severe AR alive during the follow-up period might be those exhibiting a lower impact of AR on left ventricular function. Finally, a longer follow-up might be needed to detect impairment in LVEF associated with the occurrence of moderate to severe AR.

CLINICAL IMPLICATIONS. The results of this study have important clinical implications. First, the lack of impact of mild AR on 2-year clinical outcomes suggests that additional therapeutic measures other than a systematic follow-up are not necessary in such patients. On the other hand, a careful evaluation of the baseline echocardiographic images is strongly suggested in those patients diagnosed with moderate to severe AR after TAVR. Considering the major periprocedural and late negative clinical impact associated with the occurrence of acute AR leading to an AR of a moderate to severe degree, all efforts should be made to decrease the regurgitant volume in such patients early in the postoperative period. Such measures include balloon post-dilation, implantation of a second valve, percutaneous closure of the paravalvular leak with vascular plugs, or even cardiac surgery and removal of the transcatheter valve (18–20). Also, the implantation or manipulation of a pacemaker to increase the baseline heart rate and consequently decrease the diastolic filling time might be useful to improve initial tolerance to moderate to severe AR and bridge patients from acute to chronic moderate to severe AR (40). Although these measures may be associated with potential risks and increased costs, their application seems to be justified by the dismal prognosis associated with acute moderate to severe AR after TAVR. In those patients with moderate to severe AR after TAVR but no increase in AR severity compared with baseline, a closer follow-up is probably a reasonable option, as it has been in most patients diagnosed with chronic AR. Additional measures for the treatment of paravalvular leaks in such patients should be implemented during the follow-up period if any significant deterioration in clinical status and/or ventricular function parameters occurs.

STUDY LIMITATIONS. This study had no event adjudication committee. However, although this limitation may be important for the quoting of some complications, it may be less relevant when considering the endpoint of death (yes/no). The study might be underpowered to detect significant differences in 30-day mortality between the chronic and acute moderate to severe AR groups. The assessment of AR was based on the results of transthoracic echocardiograms analyzed at each center; no Echo Core Lab was available in this study. Although echocardiographic examinations were available in all patients at baseline and during the hospitalization period, echocardiographic data were missing in as many as 29% of the patients alive at follow-up. Also, the impact of AR on left ventricular function over time might have been underestimated because of the lack of echocardiograms in patients who died within the first 6 months after TAVR. In the analysis of the impact of AR on changes in MR over time, data on the etiology of MR were not available and possible confounders were not adjusted for.

CONCLUSIONS

Residual AR is a frequent complication of TAVR. The clinical impact (increased acute and late overall and

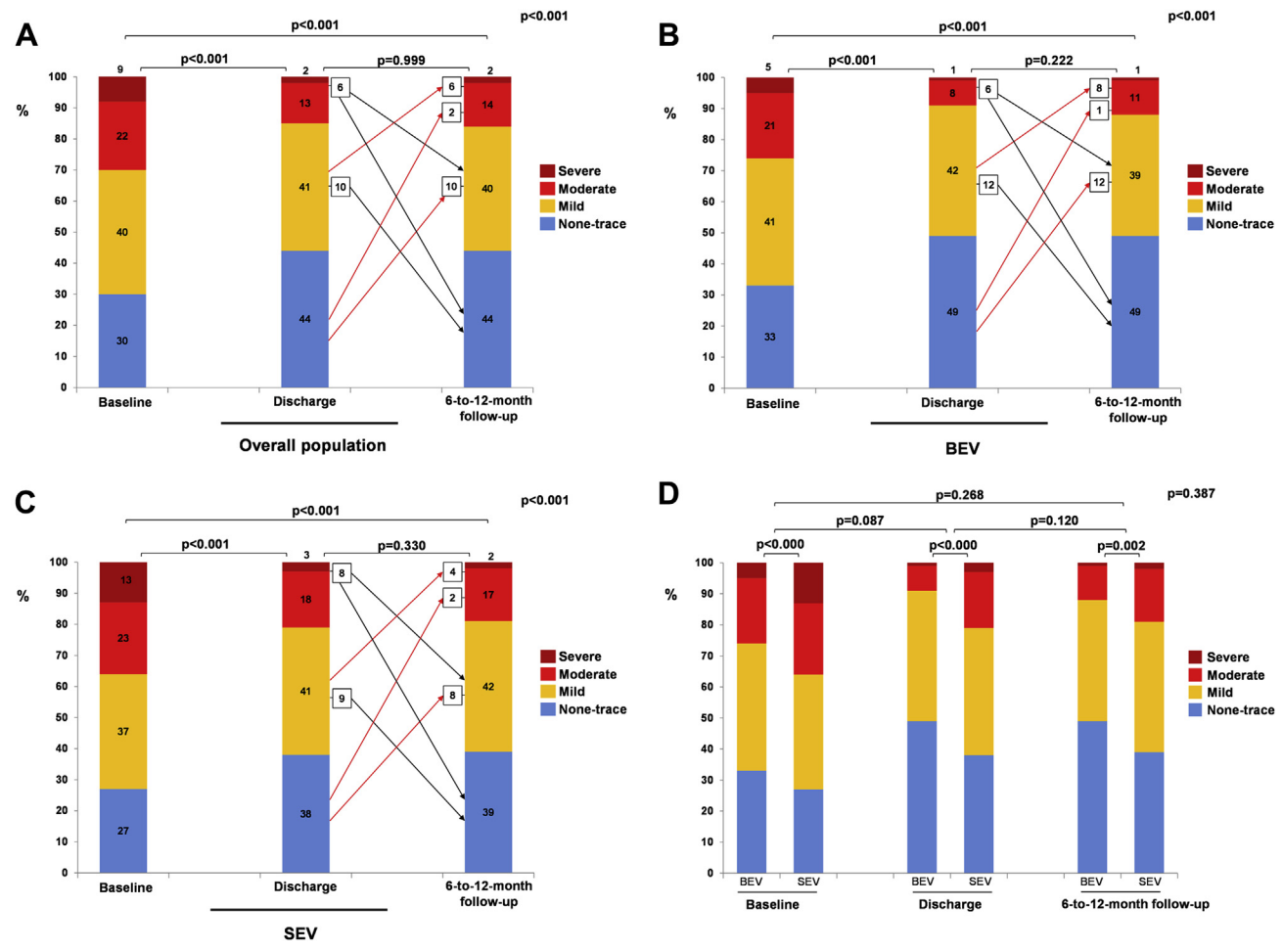


FIGURE 6 Changes in AR Over Time

Changes in aortic regurgitation (AR) in the overall population **(A)**, in the balloon-expandable valve (BEV) group **(B)**, in the self-expanding valve (SEV) group **(C)**, and comparisons between both groups **(D)**. Of note, only patients with evaluation of AR at the 3 points of time were included (N = 1,064; 543 patients in the BEV group and 521 patients in the SEV group).

cardiovascular mortality) of this complication was mainly limited to those patients with moderate to severe AR of acute origin (significant increase vs. baseline), suggesting that early additional measures for the treatment of paravalvular leaks leading to a decrease in the severity of AR in such patients are probably of major clinical importance. The final risk/benefit ratio of such a strategy will have to be determined in future studies.

ACKNOWLEDGMENT The authors thank Melanie Côté for her help in the statistical analyses and preparation of figures.

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KEY WORDS acute aortic regurgitation, aortic regurgitation, mitral regurgitation, paravalvular leak, transcatheter aortic valve implantation, transcatheter aortic valve replacement

APPENDIX For a supplemental figure, please see the online version of this article.