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Transcatheter Aortic Valve Replacement for Residual Lesion of the Aortic Valve Following "Healed" Infective Endocarditis

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ABSTRACT

OBJECTIVES This study aimed to evaluate the safety and mid-term efficacy of transcatheter aortic valve replacement (TAVR) in the setting of aortic valve (AV) infective endocarditis (IE) with residual lesion despite successful antibiotic treatment.

BACKGROUND Patients with AV-IE presenting residual lesion despite successful antibiotic treatment are often rejected for cardiac surgery due to high-risk. The use of TAVR following IE is not recommended.

METHODS This was a multicenter retrospective study across 10 centers, gathering baseline, in-hospital, and 1-year follow-up characteristics of patients with healed AV-IE treated with TAVR. Matched comparison according to sex, EuroSCORE, chronic kidney disease, left ventricular function, prosthesis type, and valve-in-valve procedure was performed with a cohort of patients free of prior IE treated with TAVR (46 pairs).

RESULTS Among 2,920 patients treated with TAVR, 54 (1.8%) presented with prior AV-IE with residual valvular lesion and healed infection. They had a higher rate of multivalvular disease and greater surgical risk scores. A previous valvular prosthesis was more frequent than a native valve (50% vs. 7.5%; $p < 0.001$). The in-hospital and 1-year mortality rates were 5.6% and 11.1%, respectively, comparable to the control cohort. After matching, the 1-year III to IV aortic regurgitation rate was 27.9% (vs. 10%; $p = 0.08$) and was independently associated with higher mortality. There was only 1 case of IE relapse (1.8%); however, 18% of patients were complicated with sepsis, and 43% were readmitted due to heart failure.

CONCLUSIONS TAVR is a safe therapeutic alternative for residual valvular lesion after successfully healed AV-IE. At 1-year follow-up, the risk of IE relapse was low and mortality rate did not differ from TAVR patients free of prior IE, but one-fourth presented with significant aortic regurgitation and >50% required re-admission.
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ABBREVIATIONS AND ACRONYMS

AV = aortic valve

IE = infective endocarditis

TAVR = transcatheter aortic valve replacement

Infective endocarditis (IE) is a life-threatening disease affecting between 1 and 10 cases per 100,000 individuals each year (1,2). Despite the improvement in its detection, management, and treatment, a rise in its incidence has occurred (3,4), and mortality and complication rates have not decreased in the last decades (4). In-hospital mortality of patients admitted with left-sided IE is between 15% and 30% depending on baseline conditions of the patients, the causative organism, and the presence of complications (5,6). Antibiotic treatment is the standard of care (5,7), but when the infection persists after appropriate antibiotic therapy, surgery is mandatory to debride the infected tissues. In about 50% of left-sided IE, despite successfully treating the infection, surgery is required during the index hospitalization in order to treat residual cardiac lesions affecting valvular function or causing periannular complications (7,8). If these conditions are not treated surgically, the prognosis is poor due to heart failure leading to early mortality in most cases. However, nearly one-third of the patients deemed surgical due to residual valvular lesion are rejected for surgery due to high operative risk (9). In this scenario, the use of percutaneous valve therapies is currently contraindicated in the guidelines. The risk of IE relapse and the poor prognosis of endocarditis affecting transcatheter valves explain such reluctance to their use in this clinical setting (10,11). Conversely, a recent study suggests that after 10 days of correct antibiotic treatment, most of the operated patients with aortic valve (AV) IE and free of *Staphylococcus aureus* infection or extension to the mitral valve, presented negative explant culture (12).

A few cases of percutaneous treatment for residual lesions after IE as peri-prosthetic leakage or mitral damage are described in the published reports with good outcomes (13,14). Also, several anecdotal cases of transcatheter aortic valve replacement (TAVR) in order to treat these residual lesions have been published to date with optimal results at follow-up (13-16). However, a systematic analysis and follow-up of these patients in order to determine the actual risk and predictors of relapse or other complications have not been performed yet. Therefore, we aimed to perform a multicenter consecutive registry of TAVR cases including all those with prior AV-IE considered healed after antibiotic therapy but with residual severe valvular lesion treated with TAVR in order to: 1) determine the incidence; 2) analyze the acute results; and 3) determine the complication rate in the follow-up with particular attention to the risk of reinfection or relapse.

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METHODS

STUDY POPULATION. All cases treated with last-generation TAVR devices between January 2015 and December 2018 in 10 institutions were retrospectively collected. In particular, patients presenting with "healed" IE treated with TAVR were gathered. The registry was approved by the ethics committee of each participating institution. Inclusion criteria included the diagnosis of possible or definitive AV-IE according to the modified Duke's criteria (17) successfully treated with antibiotics but with residual—or pre-existing—severe AV dysfunction. An adequate response to antibiotics was defined as 3 consecutive negative blood cultures, patient free of clinical/laboratory signs of sepsis, and patient also free of cardiac vegetation or abscess (18). Any doubt on persistent infection was considered an exclusion criteria for participation in the registry. Reinfection or relapse of IE were pre-defined as infection caused by a different micro-organism within the first year following the TAVR procedure (reinfection) or by the same agent (relapse) (19).

Baseline characteristics including frailty (eyeball definition) or any prior cardiovascular surgery were gathered. The following time data were collected: beginning of IE, duration between diagnosis to infection healing, and date of TAVR procedure. All procedural characteristics and related complications defined according to Valve Academic Research Consortium-2 criteria (20) were prospectively collected in each center's database where it was predefined. Type and prosthesis size, as well as vascular access, were included. Decision to implant the TAVR device and the type of device, including balloon-, self-, or mechanically expandable

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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TABLE 1 Baseline Characteristics of the Study Population

	Global Population			Matched Population		
	IE (n = 54)	Non-IE Group (n = 2,843)	p Value	Infective Endocarditis (n = 46)	Non-IE Group (n = 46)	p Value
Clinical characteristics						
Age, yrs	79.1 ± 8	80.7 ± 7.2	0.085	78.98 ± 8.20	79.62 ± 8.02	0.714
Male	31 (57.5)	1320 (46.1)	0.097	27 (58.7)	23 (50.0)	0.541
BMI, kg/m^2	28.5 ± 5.8	27.8 ± 5.0	0.381	28.1 ± 5.5	27.7 ± 5.1	0.764
Diabetes mellitus	26 (48.1)	980 (34.3)	**0.033**	20 (43.5)	24 (52.2)	0.523
Coronary artery disease	32 (59.3)	947 (36.5)	**0.001**	21 (58.3)	17 (47.2)	0.503
Previous PCI	15 (27.8)	527 (24.5)	0.583	10 (28.6)	11 (31.4)	0.999
CKD, eGFR <60 ml/min	26 (48.1)	1,113 (39.5)	0.197	21 (45.7)	22 (47.8)	0.999
COPD	19 (35.8)	661 (23.1)	**0.030**	16 (34.8)	13 (28.3)	0.664
Previous open-chest surgery	32 (59.3)	364 (13.5)	**<0.001**	25 (56.6)	18 (40.9)	0.092
Previous SVR	27 (50)	156 (7.5)	**<0.001**	22 (47.8)	19 (41.3)	0.549
Stroke/TIA	5 (9.3)	289 (11.2)	0.652	3 (6.5)	9 (19.6)	0.070
AF	22 (40.7)	882 (30.8)	0.118	20 (43.5)	15 (32.6)	0.405
Frailty	13 (24.1)	272 (9.5)	**<0.001**	11 (23.9)	5 (10.9)	0.180
STS-PROM, %	11.8 (3.5–15.1)	5.2 (3.5–8.2)	**0.003**	6.7 (3.7–14.7)	8.3 (2.8–13.2)	0.992
EuroSCORE log, %	21.2 (15.0–53.5)	12.6 (8.0–20.6)	**0.002**	19.5 (12.7–29.4)	21.3 (10.4–31.0)	0.666
Echocardiographic findings						
LVEF, %	55.8 ± 13.1	57.9 ± 13.8	0.257	56.4 ± 13.3	52.8 ± 16.3	0.274
Aortic valve area, cm^2	1.31 ± 0.75	0.66 ± 0.19	**0.047**	1.54 ± 0.87	0.56 ± 0.10	0.081
Peak gradient, mm Hg	56.7 ± 29	77.9 ± 23.7	**0.007**	48.9 ± 18.4	77.7 ± 22.5	0.052
Mean gradient, mm Hg	43.8 ± 16.5	48 ± 16.2	0.071	44.8 ± 16.5	39.4 ± 14.6	0.966
Aortic regurgitation III or IV	1 (1.9)	63 (2.9)	0.999	0 (0.0)	0 (0.0)	0.999
Mitral regurgitation III or IV	4 (7.6)	280 (10.0)	0.666	4 (9.5)	20 (47.6)	**<0.001**

Values are mean ± SD, n (%), or median (interquartile range). Significant p values are in **bold**.

BMI = body mass index; CKD = chronic kidney disease; COPD = chronic obstructive coronary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IE = infective endocarditis; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; SVR = surgical valve replacement; TIA = transient ischemic attack.

prosthesis, were determined by the heart team of each center. The procedural strategy was selected according to their own institutional protocol.

In-hospital and 1-year follow-up were specifically performed for the study after consent by each institution's ethics committee and by the patients. Specific endpoints in the follow-up were global and cardiovascular mortality, functional state according to New York Heart Association (NYHA) functional grade, sepsis criteria as defined elsewhere (21), cerebrovascular event, or embolic phenomena within the first year after discharge.

ECHOCARDIOGRAPHIC ASSESSMENT. Comprehensive transthoracic echocardiography data were obtained at baseline, before hospital discharge, and at follow-up. If performed, transesophageal echocardiographic data were also gathered. Specifically collected variables included the findings during the IE episode: pre-existing valvular dysfunction; vegetation, fistulae, abscess, or pseudoaneurysm and their location; and left ventricular ejection fraction.

Once the infection was considered healed, all pre-TAVR parameters were collected: AV area, peak and mean pressure gradients, aortic regurgitation degree, mitral valve mean gradient and degree of regurgitation, and left ventricular ejection fraction, all following the echocardiography guidelines from the European Association of Echocardiography and the American Society of Echocardiography (22). Residual lesion of the AV was considered when severe stenosis and/or severe regurgitation was determined according to same guidelines (22). Echocardiographic result before patient discharge and at 1-year follow-up were obtained again with all valvular function parameters and left ventricular ejection fraction. Particular attention to new valvular regurgitation, and evidence of vegetation or other complication suggesting valvular infection (17) were gathered.

STATISTICAL ANALYSIS. Data are expressed as absolute frequency and percentage for qualitative variables. Quantitative variables are described as mean ± SD or as median (interquartile range), depending on variable distribution. A propensity score was estimated using a logistic regression model with IE as the dependent variable, including the following variables: sex, EuroSCORE, chronic kidney disease, left ventricular ejection fraction, prosthesis type, and valve-in-valve procedure (Supplemental Figure 1).

TABLE 2 Characteristics of IE According to Affected Valve

	Global IE Population (n = 54)	Native Valve (n = 28)	Prosthetic Valve (n = 26)	p Value
IE criteria				
Fever	41 (75.9)	20 (71.4)	21 (80.8)	0.442
Vascular phenomena	2 (3.8)	2 (7.1)	0 (0.0)	0.493
Definitive IE	28 (52.8)	13 (46.4)	15 (60.0)	0.266
Possible IE	26 (51.9)	16 (53.6)	10 (40.0)	
3 consecutive (+) blood cultures	39 (72.2)	18 (64.3)	21 (80.8)	0.075
Vegetations	40 (74.1)	24 (85.7)	16 (61.5)	**0.043**
Isolated micro-organism				
Enterococcus	14 (35.9)	4 (22.2)	10 (47.6)	0.099*
Streptococcus sp.	9 (23.1)	6 (33.3)	3 (14.3)	0.255*
Staphylococcus aureus	11 (28.2)	5 (27.8)	6 (28.6)	0.956*
Fungi	1 (2.6)	1 (5.6)	0 (0.0)	0.462*
Gram-negative	2 (5.1)	0 (0.0)	2 (9.5)	0.490*
Negative coagulase	1 (2.6)	1 (5.6)	0 (0.0)	0.462*
Polymicrobial culture	1 (2.6)	1 (5.6)	0 (0.0)	0.462*

Values are n (%). Significant p values are in **bold**. *Reference micro-organism against other micro-organisms.
IE = infective endocarditis.

Pairs of patient were derived using the greedy nearest neighbor method 1:1 with one-fifth of the SD of the logit of the propensity score as caliper. The MatchIt package (Ho, Imai, King, & Stuart, 2007 package, R Core Team, Vienna, Austria) was used. Comparison of categorical and continuous variables between the matched cohorts was performed using the McNemar test and Wilcoxon rank test, respectively. Kaplan-Meier curves were used to show 1-year mortality between groups and compared with the log-rank test. The hazard ratios and 95% confidence intervals were estimated with the use of Cox proportional risk models to determine event predictors and the proportionality of the risks were checked using Schoenfeld residuals. All tests were 2-sided at the 0.05 significance level. Statistical analysis was performed with using IBM SPSS Statistics version 25 (IBM, Armonk, New York) and R core team (2019, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

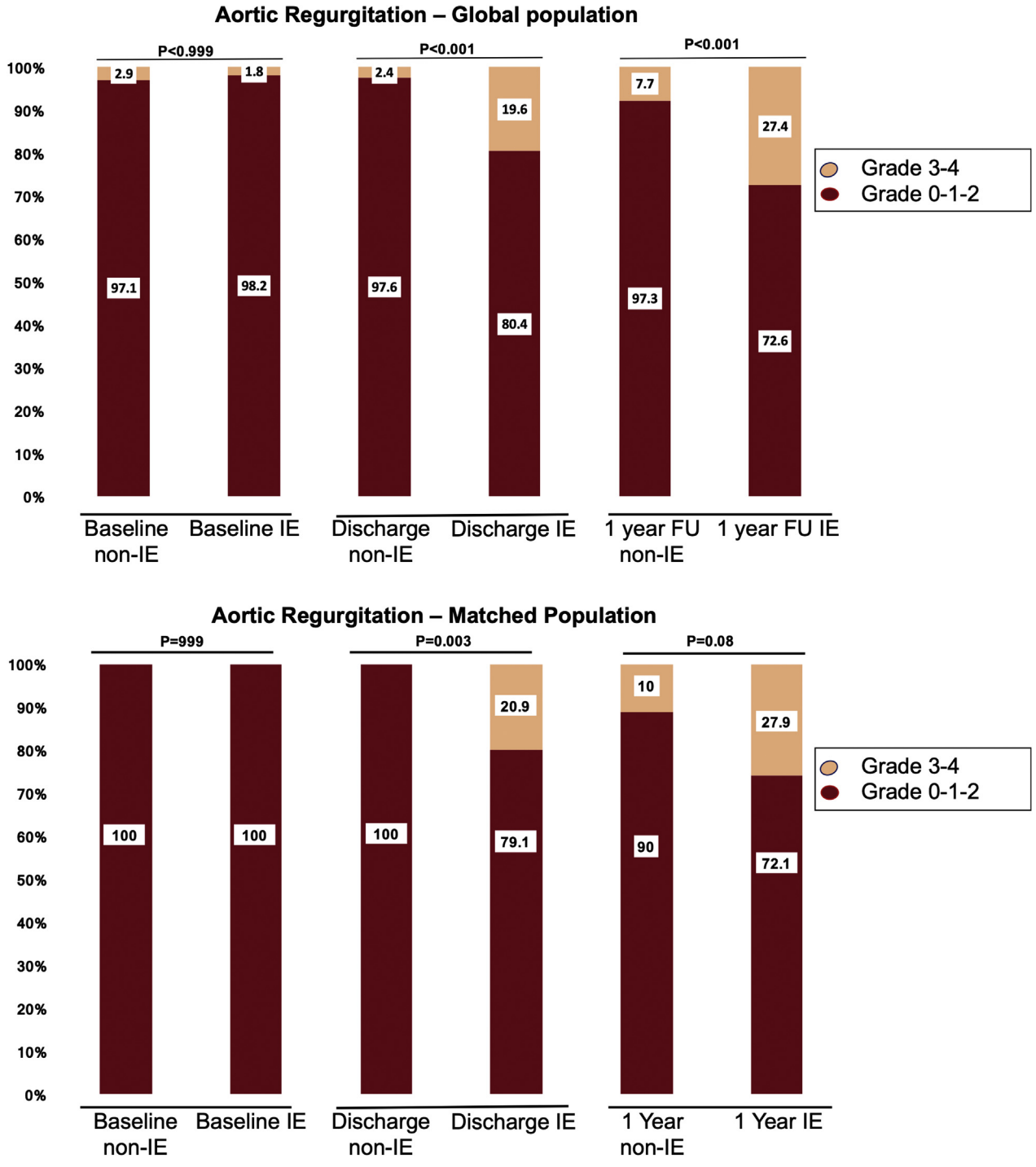
BASELINE CHARACTERISTICS AND PRIOR IE FEATURES. A total of 2,920 patients underwent TAVR during the study timeframe. Of them, 54 patients (1.8%) presented with prior diagnosis of possible (n = 26, 48.1%) or definitive (n = 28, 51.9%) IE a mean time of 90 days before the TAVR procedure, ranging between 21 and 411 days (median 62 days; interquartile range: 38 to 89 days). Clinical background and baseline echocardiographic characteristics at the time of TAVR are summarized in Table 1. Significant differences were observed in baseline characteristics between groups. Patients with prior IE had significantly more diabetes mellitus (48.1% vs. 34.3%; p = 0.033), chronic obstructive pulmonary disease (35.8% vs. 23.1%; p = 0.030), and were frailer (24.1% vs. 9.5%; p < 0.001). Although no differences existed regarding the rate of cerebrovascular events, 3.7% of the patients presented with a cerebrovascular event during the IE episode. Also, surgical risk as estimated by European System for Cardiac Operative Risk Evaluation Logistic score and Society of Thoracic Surgeons score was higher in patients with past IE.

As compared with patients free of prior IE, the IE cohort presented more often with a surgical cardiac valve prosthesis (50.0% vs. 7.5%; p < 0.001). The impact of this variable in the IE course has been specifically depicted in Table 2. The presence of vegetations during the IE episode was less common in patients harboring previous valvular prosthesis (61.5% vs. 85.7%; p = 0.043), and 3 consecutive positive blood cultures were obtained more often (80.8% vs. 64.3%; p = 0.075). The most frequent causative micro-organism was *Enterococcus* (35.9%), but negative cultures were present in 27.8% of patients. Regarding the main echocardiographic findings, patients without prior IE presented with higher aortic peak gradient (77.9 ± 23.7 mm Hg vs. 56.7 ± 29 mm Hg; p = 0.007), and greater rates of significant mitral and aortic regurgitation as shown in Figure 1, but no differences existed regarding baseline left ventricular ejection fraction. All but 1 patient—who presented with isolated aortic regurgitation due to leaflet perforation—were diagnosed with moderate (n = 6, 11.1%) or severe (n = 46, 85.2%) aortic stenosis; of these, 15 patients (27.8%) had concomitant moderate aortic regurgitation. Presence of pseudoaneurysms of leaflet perforation was described in 7 (13%) and 2 (3.7%) patients, respectively. Several examples of the mechanism of residual lesions following IE and their successful treatment with TAVR are depicted in Figure 2 and Video 1.

After propensity score matching, 46 patients with prior IE and 46 with degenerative aortic stenosis constituted the matched population (n = 92). As shown in Table 1, main baseline characteristics were well balanced between both matched groups except for the rate of residual mitral regurgitation.

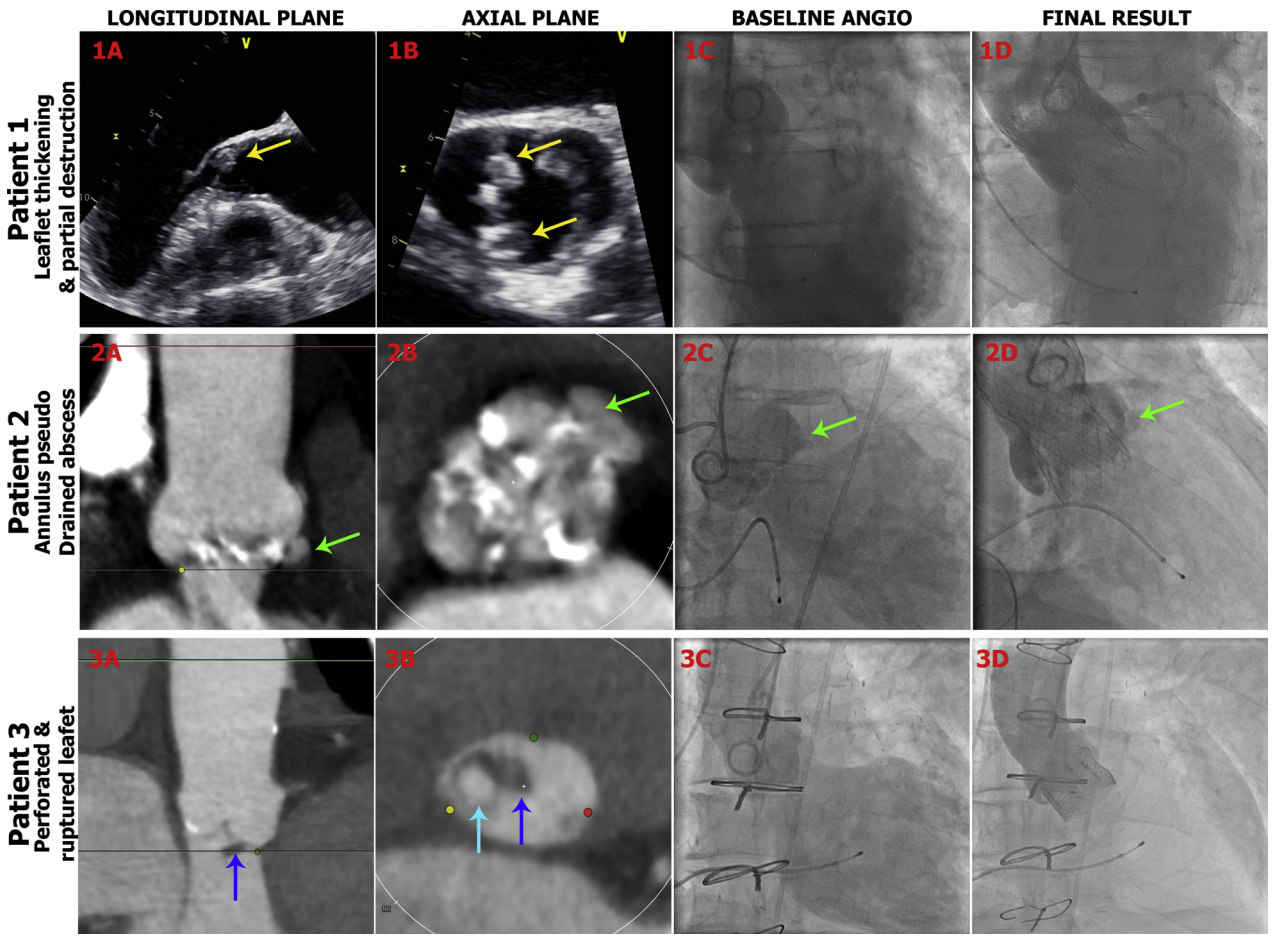
PROCEDURAL AND IN-HOSPITAL OUTCOMES. The main procedural and in-hospital outcomes are reported in Table 3. Echocardiographic findings at discharge are summarized in Table 4. The presence of prior IE was associated with a lower rate of balloon pre-dilatation (6.0% vs. 60.0%; p < 0.001) and post-dilatation (3.7% vs. 25.7%; p < 0.001) compared with

FIGURE 1 Aortic Regurgitation at Baseline, Discharge, and at 1-Year Follow-Up



Aortic regurgitation at baseline, discharge, and at 1-year follow-up (FU) in patients receiving transcatheter aortic valve replacement (TAVR) due to residual valvular lesion after infective endocarditis (IE) and for the global TAVR population. **(A)** Unmatched cohorts. **(B)** Matched cohorts.

FIGURE 2 Mechanisms of AV Dysfunction Following IE, Successfully Treated With TAVR Devices



Patient #1: Transesophageal echocardiography showing leaflet thickening and partial destruction **(1A and 1B, yellow arrows)**; after 4 weeks of antibiotics, significant aortic stenosis and moderate aortic regurgitation persisted (angiography, **1C**). TAVR was successfully performed with a 34-mm Evolut-R (Medtronic, Minneapolis, Minnesota) with no residual aortic regurgitation (angiography, **1D**). Patient #2: cardiac-computed tomography demonstrated a small pseudoaneurysm of the aortic annulus between the left and right coronary sinuses with moderate regurgitation and stenosis **(2A and 2B, green arrows)**. **Green arrows in 2C and 2D** indicate the presence of a pseudoaneurysm. Three weeks after completing antibiotics, a 29-mm Evolut-Pro (Medtronic) was successfully implanted (angiography, **1C and 1D**). Patient #3: Perforated **(sky blue arrow)** and ruptured leaflet **(deep blue arrow)** following aortic endocarditis (computed tomography, **3A and 3B**). Four weeks after treatment, a Lotus Edge (Boston Scientific, Marlborough, Massachusetts) valve was successfully deployed despite total absence of calcium (angiography, **3A and 3B**). AV = aortic valve; other abbreviations as in Figure 1.

the global TAVR population. However, at discharge, the rate of moderate or severe aortic regurgitation was significantly higher for patients with prior IE (19.6% vs. 2.4%; $p < 0.001$) (Figure 1). No differences were found regarding the type of TAVR device, including self- (68.0%), balloon- (28.3%), or mechanically expanded valves (3.7%).

There were no significant differences in the rate of global procedural complications (20.4% vs. 15.6%; p = NS); in particular, vascular complications (5.6% vs. 6.4%; p = NS), major bleeding (9.3% vs. 5.7%; p = NS), and permanent pacemaker implantation (16.7% vs. 20.9%; p = ns) rates did not differ. The in-hospital mortality rates (5.6% and 5.1%; p = NS) was comparable between both groups. Although no cases of in-hospital TAVR device infection were reported, 7 patients presented with sepsis during the hospital stay (13.0% vs. 7.5% in the group without prior IE; p = 0.184), and 2 of them died in relation with this complication. In all cases, a respiratory infection was considered the origin of the sepsis, but relapse could not be excluded in 1 of the patients who died due to rapid deterioration that precluded transesophageal echocardiography or blood cultures.

TABLE 3 Procedural Characteristics of the TAVR Implantation, Complications, and Echocardiographic Parameters During Hospitalization

	Global Population			Matched Population		
	IE Group (n = 54)	Non-IE Group (n = 2,866)	p Value	IE Group (n = 46)	Non-IE Group (n = 46)	p Value
Procedural characteristics						
Balloon pre-dilation	3 (6.0)	1659 (60)	**<0.001**	2 (5.3)	21 (55.4)	**<0.001**
Balloon post-dilation	2 (3.7)	677 (25.7)	**<0.001**	2 (4.7)	9 (20.9)	0.065
Procedural complication*	11 (20.4)	165 (15.6)	0.350	6 (4.4)	1 (2.2)	0.999
Valve embolization	2 (3.7)	48 (2.0)	0.310	2 (4.4)	2 (4.4)	0.999
In-hospital complications						
Length of stay	8 (6–11)	6.5 (5–9)	**0.001**	8 (6–11)	7 (6–15)	0.194
In-hospital mortality	3 (5.6)	147 (5.1)	0.756	3 (6.5)	5 (10.9)	0.727
Sepsis	7 (13.0)	89 (7.5)	0.184	4 (15.4)	4 (15.4)	0.999
Major vascular complication	3 (5.6)	181 (6.4)	0.999	2 (4.3)	3 (6.5)	0.999
Major bleeding	5 (9.3)	161 (5.7)	0.240	4 (8.7)	1 (2.2)	0.375
Myocardial infarction	4 (7.4)	32 (1.4)	**0.009**	4 (10.8)	2 (5.4)	0.687
Stroke/TIA	2 (3.7)	68 (2.4)	0.382	2 (4.7)	2 (4.7)	0.999
Permanent pacemaker implantation	9 (16.7)	541 (20.9)	0.448	7 (17.1)	5 (12.2)	0.754
New LBBB	6 (11.1)	210 (11.8)	0.877	3 (8.6)	6 (17.1)	0.508
Echocardiographic parameters at in-hospital assessment						
LVEF, %	55.9 ± 13	59.7 ± 12.5	**0.039**	55.9 ± 13.6	55.9 ± 15.6	0.982
Mean gradient, mm Hg	11.4 ± 5.7	9.7 ± 5.6	**0.022**	11.5 ± 6.1	11.6 ± 4.9	0.966
Aortic valve area, cm^2	1.6 ± 0.37	1.7 ± 0.7	0.734	1.7 ± 0.4	1.4 ± 0.5	0.350
AR grade III or IV, %	10 (19.6)	61 (2.4)	**<0.001**	7 (20.9)	0 (0.0)	**0.003**
MR grade III or IV, %	18 (34.0)	139 (6.9)	**<0.001**	15 (41.7)	2 (5.6)	**0.001**

Values are n (%), median (interquartile range), or mean ± SD. Significant p values are in **bold**. *Procedural complications are defined as any clinical condition that results in hemodynamic instability such as rapid new-onset atrial fibrillation, pulmonary edema, valve malpositioning, and vascular access site and access-related complications according to definitions stablished in VARC-2 criteria.

AR = aortic regurgitation; LBBB = left bundle branch block; MR = mitral regurgitation; TAVR = transcatheter aortic valve replacement; other abbreviations as in Table 1.

MAIN 1-YEAR FOLLOW-UP CLINICAL AND ECHOCARDIOGRAPHIC OUTCOMES. Median follow-up was 404 days (interquartile range: 348 to 734 days), and 100% of the patients had completed 1-year follow-up or died within that time. The 1-year mortality rate was 11.1%, and was comparable to the control cohort (10.0%; p = 0.790); after matching for baseline differences, the lack of differences in the mortality persisted as depicted in Figure 3. The main independent predictors of mortality for the global study population are summarized in Table 5; the presence of prior IE was not among them, but the presence of moderate or severe aortic regurgitation (27.5% at 1-year follow-up vs. 7.7%; p < 0.001) (Figure 1) was associated with a higher mortality rate (hazard ratio: 2.11; 95% confidence interval: 1.12 to 4.00; p = 0.022).

At 1-year follow-up, 3 more patients in the prior IE group presented with sepsis, bringing the total number of patients with sepsis in the IE group to 10 (18.5%). All 3 cases died, 2 of them due to alternative infective complications (pneumonia and urinary sepsis) with causative micro-organisms different from those of the IE. The third patient presented with

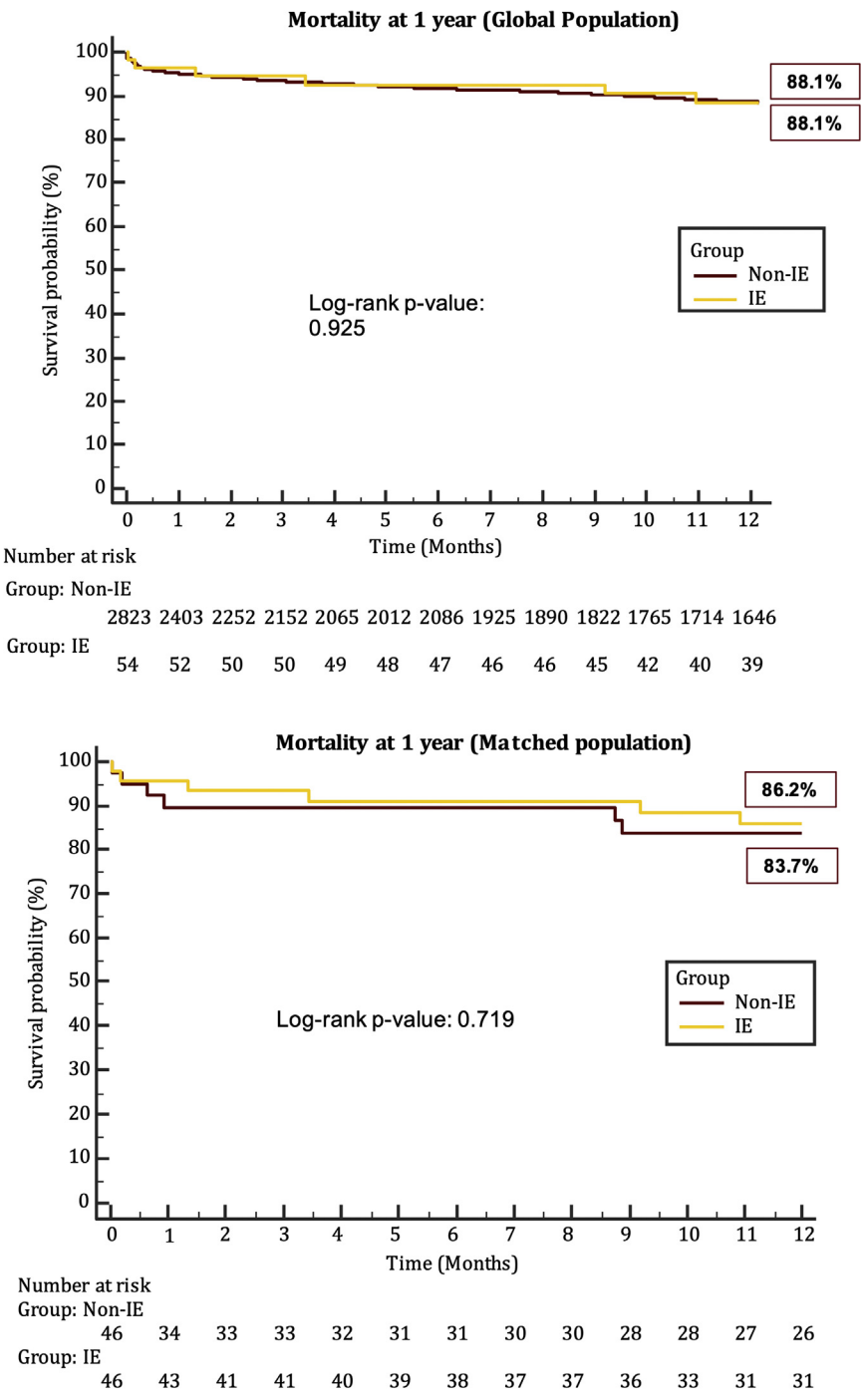
TABLE 4 Echocardiographic and Clinical Outcomes at 1-Year Follow-Up

	Global Population			Matched Population		
	IE Group (n = 54)	Non-IE Group (n = 2,866)	p Value	IE Group (n = 46)	Non-IE Group (n = 46)	p Value
Echocardiographic parameters at 1-yr follow-up						
LVEF, %	55.8 ± 12	59.5±11.3	**0.015**	54.7 ± 13.2	56 ± 12.8	0.706
Mean gradient, mm Hg	15 ± 8.5	9.8±7.1	**<0.001**	14.3 ± 7	12.9 ± 5.8	0.458
Aortic valve area, cm^2	1.67 ± 0.49	1.65 ± 0.47	0.843	1.75 ± 0.21	1.58 ± 0.53	0.795
AR grade III or IV, %	14 (27.5)	145 (7.7)	**<0.001**	7 (25.9)	3 (11.1)	0.289
MR grade III or IV, %	26 (49.1)	212 (14.3)	**<0.001**	14 (58.3)	5 (20.8)	**0.035**
Clinical outcomes						
NYHA functional class III or IV, %	10 (19.6)	149 (11.0)	0.055	3 (12.0)	2 (8.0)	0.999
Cumulative 1-yr mortality, KM rate	6 (11.1)	287 (10.0)	0.925	6 (13.0)	6 (13.0)	0.719

Values are mean ± SD or n (%). Significant p values are in **bold**.

AR = aortic regurgitation; KM = Kaplan-Meier; NYHA = New York Heart Association; other abbreviations as in Tables 1 and 3.

FIGURE 3 Survival Curves for the Patients Receiving TAVR After IE and for the Global TAVR Population



Survival curves for the patients receiving TAVR due to residual valvular lesion after infective endocarditis and for the global TAVR population. **(A)** Unmatched cohorts. **(B)** Matched cohorts. Abbreviations as in Figure 1.

TABLE 5 Predictors of Global Mortality at 1-Year Follow-Up in the Study Population

	Global Population (N = 2,920)			Multivariate Analysis	
	Alive at 1-Yr Follow-Up (n = 2,627)	Dead at 1-Yr Follow-Up (n = 293)	p Value	HR (95% CI)	p Value
Baseline characteristics					
Age, yrs	80.65 ± 7.21	81.43 ± 7.24	0.081	–	
Female	1,419 (54.0)	150 (51.2)	0.358	–	
Chronic kidney disease	1,003 (38.8)	136 (46.9)	**0.008**	**1.43 (1.07–1.91)**	**0.014**
COPD	602 (23.0)	78 (26.6)	0.162		
Previous coronary artery disease	865 (36.6)	114 (40.4)	0.206	–	
Previous PCI	470 (24.1)	72 (28.7)	0.111	–	
Previous open-heart surgery	357 (14.4)	39 (13.8)	0.789	–	
Previous CABG	216 (9.2)	25 (9.2)	0.975	–	
Previous valve surgery	163 (8.4)	20 (10.3)	0.379	–	
Peripheral vascular disease	264 (11.2)	50 (18.2)	**0.001**	**1.75 (1.22–2.51)**	**0.003**
Previous stroke/TIA	252 (10.7)	42 (15.3)	**0.021**	–	
Prior atrial fibrillation	789 (30.1)	115 (39.2)	**0.001**	**1.39 (1.04–1.86)**	**0.028**
Frailty	249 (9.5)	36 (12.3)	0.124	–	
STS-PROM	5.00 [3.40–7.57]	6.30 [4.47–11.40]	**<0.001**	–	
EuroSCORE log	13.57 [8.46–21.33]	16.74 [9.43–26.20]	**<0.001**	–	
NYHA functional class III or IV	1453 (62.7)	190 (71.2)	**0.003**	–	
Prior AV infective endocarditis	48 (1.8)	6 (2.0)	0.790	–	
Baseline echocardiographic parameters					
Aortic valve area, cm^2	0.70 [0.52–0.80]	0.60 [0.50–0.80]	**0.018**	–	
Mean transaortic gradient, mm Hg	46 [39–57]	44.8 [36–57]	0.212	–	
Procedural data					
Valve-in-valve procedure	162 (8.4)	20 (10.3)	0.365	–	
Embolic protection device	41 (1.9)	8 (3.8)	0.071	–	
Balloon valvuloplasty	1,485 (58.7)	177 (62.1)	0.264	–	
Post-dilatation	618 (25.3)	61 (24.0)	0.644	–	
Valve embolization	42 (1.9)	8 (3.8)	0.077	–	
Coronary artery occlusion	11 (0.5)	8 (2.9)	**<0.001**	–	
Annulus rupture	2 (0.1)	13 (4.7)	**<0.001**	–	
Tamponade	19 (1.0)	13 (6.7)	**<0.001**	–	
Conversion to open surgery	11 (0.5)	13 (4.7)	**<0.001**	–	
Echocardiographic parameters at discharge					
Left ventricular ejection fraction, %	60 [50–67]	60 [50–66]	0.518	–	
AR grade III or IV	61 (2.6)	10 (4.7)	0.066	**2.11 (1.12–4.00)**	**0.022**
In-hospital outcomes					
Sepsis	69 (6.1)	27 (24.5)	**<0.001**	**1.97 (1.34–3.18)**	**0.006**
New-onset atrial fibrillation	125 (6.3)	22 (13.6)	**<0.001**	–	
Permanent pacemaker implantation	501 (21.1)	49 (18.6)	0.341	–	
Major bleeding	127 (4.9)	39 (14.0)	**<0.001**	**1.90 (1.20–2.99)**	**0.006**
Minor bleeding	245 (12.6)	28 (13.9)	0.598	–	
Major vascular complication	138 (5.3)	46 (16.3)	**<0.001**	**2.31 (1.44–3.69)**	**<0.001**

Values are mean ± SD, n (%), or median [interquartile range]. Significant p values are in **bold**.

AV = aortic valve; CABG = coronary artery bypass graft; CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1, 3, and 4.

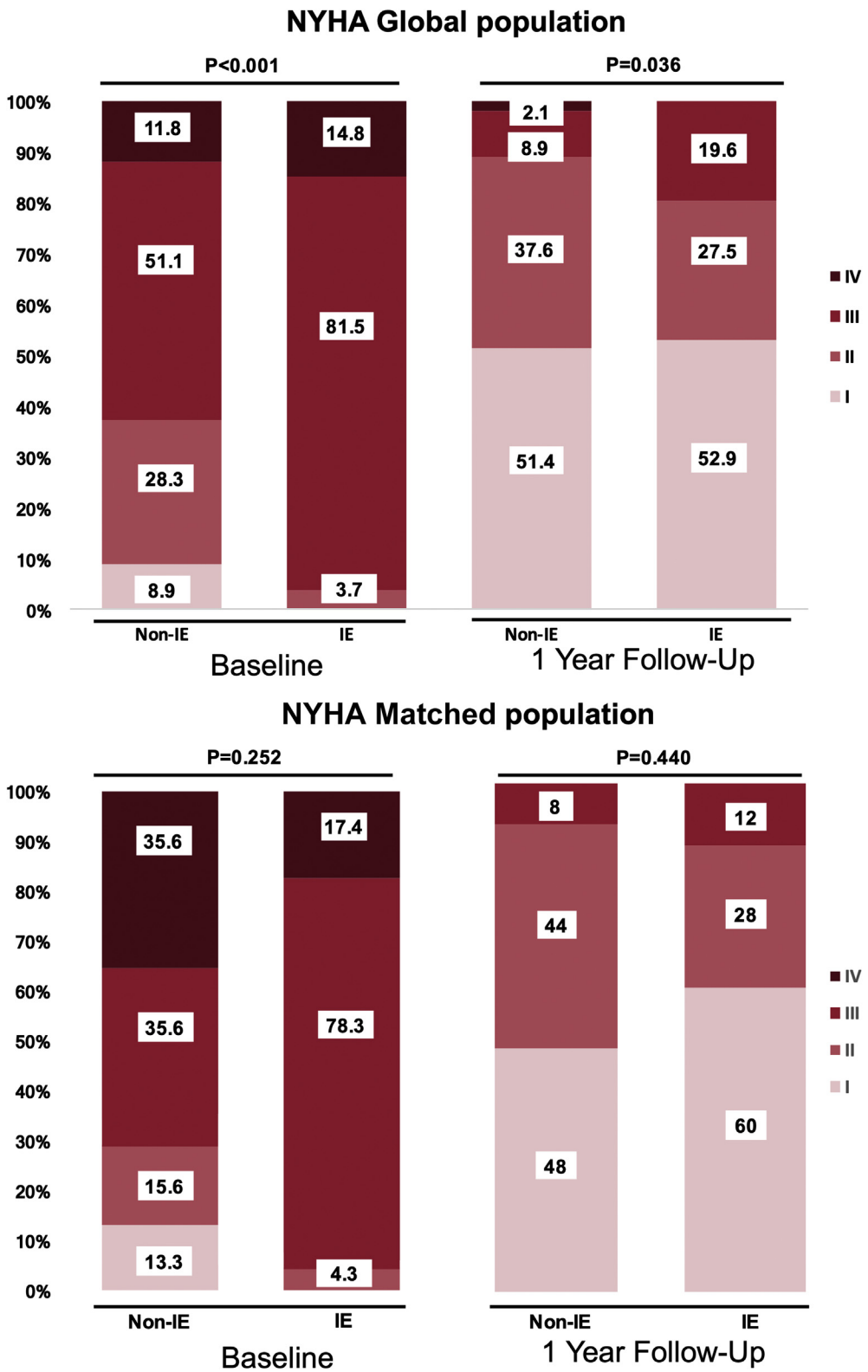
a confirmed IE relapse 20 days after TAVR with a periprosthetic abscess. Due to the very high operative risk, the patient was treated long term with antibiotics for 6 months but finally died from septic shock. In this case, the initial micro-organism identified during the IE episode was a methicillin-resistant *S. aureus*, and the TAVR procedure had been performed 87 days after that episode without any symptoms, cultures, or imaging findings (by echocardiography) suggesting persistent infection. However, the patient had developed a new significant mitral regurgitation that persisted at the time of TAVR procedure.

Supplemental Table 1 shows baseline and periprocedural characteristics in patients with prior IE according to the presence of sepsis. Two patients (3.7%) presented with stroke, and 42.8% were readmitted due to heart failure. A total of 10 patients (18.5%) remained in New York Heart Association functional class III at 1-year follow-up (**Figure 4**).

DISCUSSION

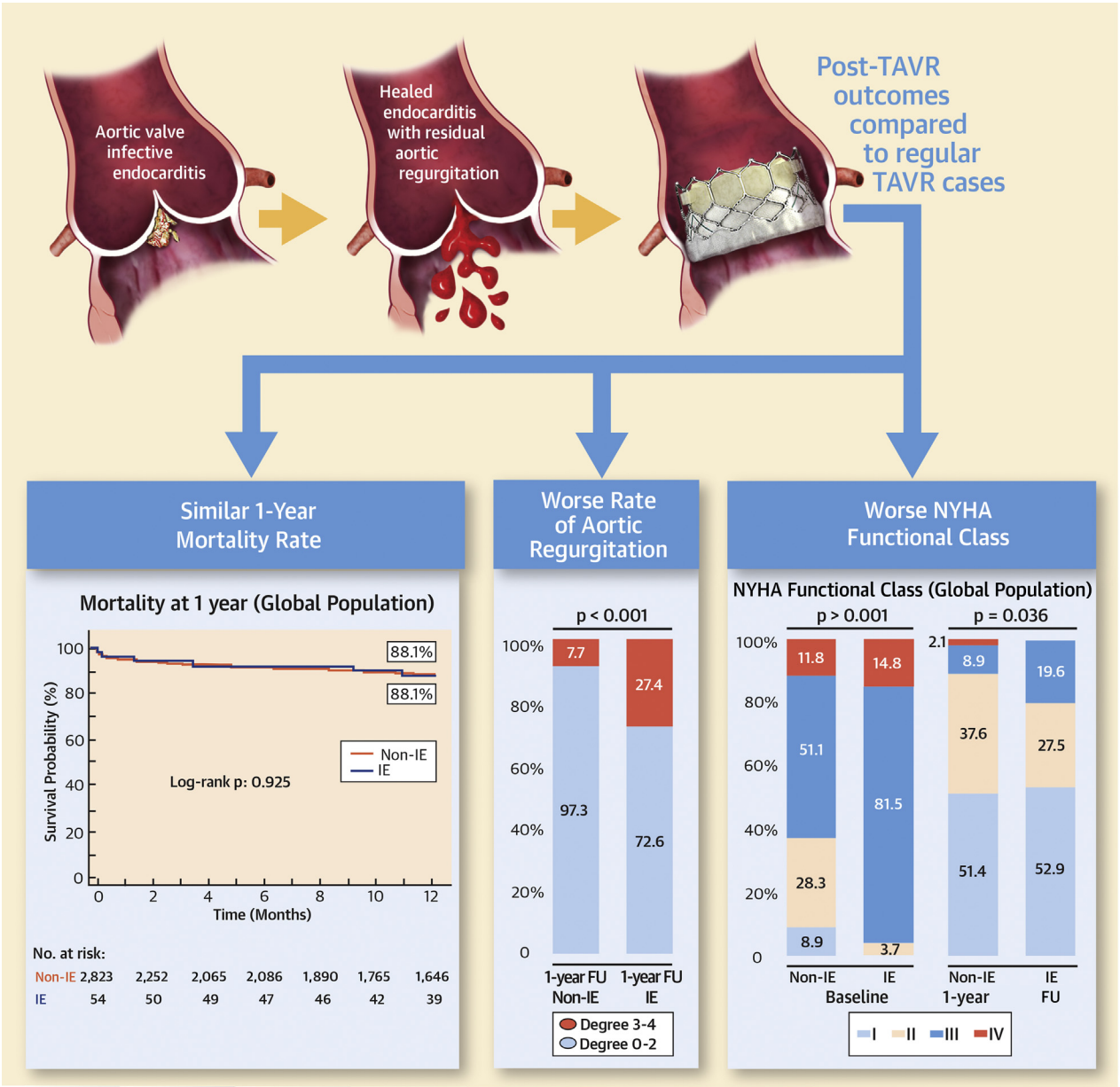
Although caution must always guide our clinical practice, a complex, comorbid, and aged population with cardiovascular conditions is increasingly treated

FIGURE 4 NYHA Functional Class at Baseline and Follow-Up



New York Heart Association functional class at baseline and follow-up for the patients receiving TAVR due to residual valvular lesion after infective endocarditis and for the global TAVR population. NYHA = New York Heart Association; other abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Main Outcomes Following Transcatheter Aortic Valve Replacement After Healed Aortic Valve Infective Endocarditis**



Santos-Martínez, S. et al. J Am Coll Cardiol Intv. 2020;13(17):1983–96.

FU = follow-up; IE = infective endocarditis; NYHA = New York Heart Association; TAVR = transcatheter aortic valve replacement.

thanks to technological advances that allow less cumbersome interventions. IE perfectly represents such challenging conditions and the poor results of conservative management that force us to find disruptive solutions. A severely damaged AV following IE results in a high 1-year mortality rate if left untreated, which has led to the controversial use of TAVR in this setting despite its formal contraindication and the lack of evidence in this context. This multicenter registry represents the first systematic

analysis reporting current outcomes of TAVR for the treatment of aortic IE residual lesion, and the main findings are summarized in the **Central Illustration**. 1) TAVR procedure may be considered as a valid therapeutic option in selected cases of IE with low risk of local infection at the time of the planned intervention and when validated risk scales discourage surgical replacement; in this setting, similar 1-year mortality compared with global population undergoing TAVR was observed. 2) However, more than 18% of these patients developed sepsis within the first year following TAVR, with only 1 case (1.8%) presenting with IE relapse. 3) Significant functional recovery was observed during follow-up, but almost one-fifth of the patients remained in NYHA functional class III or IV at 1-year follow-up, and 27.5% developed moderate or severe aortic regurgitation that was related to greater mortality.

AV-IE IN THE CURRENT ERA. AV endocarditis is frequently caused by *Streptococci* in cases of native valve endocarditis, and *Staphylococci* in patients with prosthetic valve endocarditis (6), which is consistent with our findings (23). Although infrequent, aortic IE is still a life-threatening entity with certain recent improvements in its diagnosis and treatment that have been revealed to be insufficient to improve prognosis. Due to subsequent valvular damage or IE affecting a valve with pre-existing impaired function, microbial eradication is not always enough to achieve patient recovery. Thus, patients with severe aortic residual lesion at prohibitive risk for open-heart AV replacement have a very high risk of mortality (~80% at 1 year) (24). In particular, the elderly population has a greater risk of a certain degree of AV disease at baseline and is often exposed to health care-associated infections, which together lead to an increased susceptibility to IE. TAVR constitutes an alternative treatment for this group of patients, albeit European guidelines contraindicate this option (5) due to the potential dreadful consequences of prosthesis overinfection as shown in a recent series of IE after TAVR (11,23). Amat-Santos et al. (23) reported a low incidence of IE after TAVR (0.67%), but a mortality rate above 50%. Regueiro et al. (11) described, in a large registry including more than 20,000 patients with TAVR, an incidence of IE of ~1% per person-year also with an in-hospital mortality of 36%. This evidence has led most clinicians to avoid TAVR after IE. However, recent studies show that current antibiotic regimes are effective, allowing an infected valve to become sterile in a high proportion of patients (12), which suggests that most of the patients with residual lesion of the AV after IE could receive a TAVR device relatively safely. Although the actual number of patients whose condition was complicated with AV endocarditis within the study timeframe and were treated conservatively was not recorded and is beyond our aim, this information was available in 7 of the 10 participating institutions; from a total of 1- cases with AV-IE, 7 also presented with involvement of the mitral valve and died within the hospital admission. In the remaining 3 cases, 1 had signs of persistent infection and died, and the 2 cases whose infection was healed, presented with residual pure aortic regurgitation of moderate degree. At 6 months follow-up, one was alive, and the other died due to a stroke. This information, though partial, is in agreement with the poor outcomes previously reported for medically managed AV-IE (23).

FACTORS AFFECTING THE PROGNOSIS IN TAVR RECIPIENTS FOLLOWING IE. Despite the positive global outcomes of our study population, several factors affect the prognosis and merit further analysis.

First, patients presented with a high sepsis rate (18.5%) in the first year after TAVR in the post-IE population, which poorly compares with the TAVR procedure in conventional scenarios (1.5%) (25). Indeed, post-TAVR in-hospital sepsis led to death in 2 cases (3.7%), although no hint of IE relapse was found in either. It is crucial to understand the predictive factors of relapse and the mortality predictors if this invasive strategy is selected. As previously mentioned, García-Granja et al. (12) suggested that *S. aureus* and mitral involvement were predictors of a high risk of nonsterile valve by the time of valvular replacement. Caution is therefore necessary in this setting if a TAVR procedure is considered. Indeed, these conditions were present in the only case complicated with IE relapse after TAVR. In particular, the presence of mitral regurgitation was very common in patients with a prior episode of IE although its relationship with that episode remains unclear. The new-onset mitral regurgitation during the IE episode suggests a potential extension to the mitroaortic continuity as in the described case. Whereas persistent mitral regurgitation following TAVR is a known independent marker of higher mortality (26), it may also add a greater risk of relapse if meticulous analysis of local persistent infection is not performed before planning the TAVR procedure. Particularly useful tools in this context can be ^{18}F-fluorodeoxyglucose positron emission tomography and single-photon emission computed tomography (27), but the ability of these tests to detect inactive or subclinical infection in order to prevent TAVR infection in this

context has never been investigated. In the absence of clear predictive factors, patients with significant mitral regurgitation, especially if unknown before the IE, should be excluded from TAVR.

Although a higher rate of post-procedural aortic regurgitation might be acceptable in this scenario compared with conventional TAVR indications, we have to bear in mind that it is a well-known mortality predictor. There are several reasons that may explain the greater rate of this complication and are, therefore, potential targets for improving the results: First, lower use of pre- and post-dilatation is probably related to the fear of embolizing debris from the damaged valve; however, such risk is probably very low once the infection is healed, and therefore, post-dilation should be considered if the result is suboptimal. Second, a greater rate of periprosthetic regurgitation has been reported following TAVR procedure in noncalcified cases with pure aortic regurgitation when compared with severe aortic stenosis; in this regard, only the development of new devices might improve the results (28). Finally, periprosthetic leak could be caused by the periannular sequelae of the IE that may both hinder the measurements of the aortic annulus by computed tomography and preclude adequate sealing. In this setting, 3-dimensional echocardiography might be helpful for better valve sizing.

Despite all these factors, our findings suggest that TAVR is the only therapeutic option in very high-risk surgical patients with healed IE but severe valvular residual lesion. In lower-risk patients, prospective and comparative studies with open-chest surgery are necessary. Negative cultures were noted in more than one-fourth of patients in our study, which is a high proportion compared with other IE series (2). Furthermore, the rate of definitive IE was relatively low (51.9%). This suggests a potential selection bias for the use of TAVR following an IE episode, but also highlights the safety of this strategy when the causative micro-organism is unclear following definitive or possible IE of the AV. Finally, no difference in 1-year mortality was found between patients with definitive (10.7%) or possible IE (11.5%; p = NS).

STUDY LIMITATIONS. The main limitations of the present study include its retrospective nature and the limited number of cases. Larger registries are necessary; however, our results suggest that TAVR may be an effective therapeutic option in these high-risk patients. Also, the relatively short length of the follow-up precludes further conclusions regarding the long-term outcomes. The proportion of patients with AV-IE in the participating institutions who were deemed not suitable for surgical or percutaneous treatment is unknown, and therefore, the prognosis of that strategy was not explored although previous research suggests very poor outcomes.

CONCLUSIONS

Whereas the presence of aortic IE is an absolute contraindication for TAVR, its use in patients with residual/pre-existing aortic lesion following "healed" IE, when conventional surgical AV replacement is rejected, was feasible, safe, and with comparable in-hospital and 1-year follow-up outcomes to that of the standard TAVR recipients despite higher rates of sepsis, heart failure, and residual aortic regurgitation that might result in worse outcomes at longer term.

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PERSPECTIVES

WHAT IS KNOWN? Patients with aortic valve (AV) infective endocarditis (IE) presenting residual lesion despite successful antibiotic treatment are often rejected for cardiac surgery due to high risk.

WHAT IS NEW? In selected patients with residual aortic lesion following "healed" IE, when conventional surgical valve replacement (SAVR) is rejected, the TAVR procedure may be considered a valid therapeutic option with similar in-hospital and 1-year mortality rates compared with standard TAVR procedures.

WHAT IS NEXT? Evaluation of TAVR versus SAVR for the treatment of residual lesion after AV endocarditis is warranted.

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KEY WORDS aortic prosthesis, high surgical risk, infective endocarditis, TAVR

APPENDIX For a supplemental figure, table, and video, please see the online version of this paper.