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Association Between Transcatheter Aortic Valve Replacement and Subsequent Infective Endocarditis and In-Hospital Death

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IMPORTANCE Limited data exist on clinical characteristics and outcomes of patients who had infective endocarditis after undergoing transcatheter aortic valve replacement (TAVR).

OBJECTIVE To determine the associated factors, clinical characteristics, and outcomes of patients who had infective endocarditis after TAVR.

DESIGN, SETTING, AND PARTICIPANTS The Infectious Endocarditis after TAVR International Registry included patients with definite infective endocarditis after TAVR from 47 centers from Europe, North America, and South America between June 2005 and October 2015.

EXPOSURE Transcatheter aortic valve replacement for incidence of infective endocarditis and infective endocarditis for in-hospital mortality.

MAIN OUTCOMES AND MEASURES Infective endocarditis and in-hospital mortality after infective endocarditis.

RESULTS A total of 250 cases of infective endocarditis occurred in 20 006 patients after TAVR (incidence, 1.1% per person-year; 95% CI, 1.1%-1.4%; median age, 80 years; 64% men). Median time from TAVR to infective endocarditis was 5.3 months (interquartile range [IQR], 1.5-13.4 months). The characteristics associated with higher risk of progressing to infective endocarditis after TAVR was younger age (78.9 years vs 81.8 years; hazard ratio [HR], 0.97 per year; 95% CI, 0.94-0.99), male sex (62.0% vs 49.7%; HR, 1.69; 95% CI, 1.13-2.52), diabetes mellitus (41.7% vs 30.0%; HR, 1.52; 95% CI, 1.02-2.29), and moderate to severe aortic regurgitation (22.4% vs 14.7%; HR, 2.05; 95% CI, 1.28-3.28). Health care–associated infective endocarditis was present in 52.8% (95% CI, 46.6%-59.0%) of patients. *Enterococci* species and *Staphylococcus aureus* were the most frequently isolated microorganisms (24.6%; 95% CI, 19.1%-30.1% and 23.3%; 95% CI, 17.9%-28.7%, respectively). The in-hospital mortality rate was 36% (95% CI, 30.0%-41.9%; 90 deaths; 160 survivors), and surgery was performed in 14.8% (95% CI, 10.4%-19.2%) of patients during the infective endocarditis episode. In-hospital mortality was associated with a higher logistic EuroSCORE (23.1% vs 18.6%; odds ratio [OR], 1.03 per 1% increase; 95% CI, 1.00-1.05), heart failure (59.3% vs 23.7%; OR, 3.36; 95% CI, 1.74-6.45), and acute kidney injury (67.4% vs 31.6%; OR, 2.70; 95% CI, 1.42-5.11). The 2-year mortality rate was 66.7% (95% CI, 59.0%-74.2%; 132 deaths; 115 survivors).

CONCLUSIONS AND RELEVANCE Among patients undergoing TAVR, younger age, male sex, history of diabetes mellitus, and moderate to severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis. Patients who developed endocarditis had high rates of in-hospital mortality and 2-year mortality.

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Supplemental content

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Infective endocarditis following surgical valve replacement occurs in 1% to 6% of patients and is associated with high morbidity and mortality.[1] Transcatheter aortic valve replacement (TAVR) has emerged as a therapeutic option for patients with aortic stenosis who are considered to be at high or prohibitive surgical risk.[2] The rate of infective endocarditis within the year following TAVR has been reported to be 1.5%, ranging from 0.5% to 3.1%,[3,4] similar to infective endocarditis rates after surgical valve replacement.[5,6] Greater exposure to health care procedures, older age, and a considerable amount of foreign material (eg, stent struts) of the transcatheter valve prostheses may have contributed to increase the risk of infective endocarditis in such patients. To date, data on infective endocarditis after TAVR have been limited to case reports and relatively small series with limited follow-up,[3,4,7-10] demonstrating in-hospital complication and mortality rates as high as 87% and 47%, respectively. Valve explantation rates in such patients remain relatively low (<10%). It is therefore relevant to further investigate the factors associated with and the clinical characteristics and outcomes of infective endocarditis after TAVR.

The objective of this study was to determine the clinical characteristics and outcomes of patients who develop infective endocarditis after undergoing TAVR.

Key Points

Question What are the clinical characteristics, management, outcomes, and factors associated with infective endocarditis after transcatheter aortic valve replacement (TAVR)?

Findings In this multicenter registry that included 250 cases of definite infective endocarditis after TAVR, the in-hospital mortality was 36% and the 2-year mortality rate was 66.7%. In a subset of 108 cases of infective endocarditis after TAVR younger age, male sex, history of diabetes mellitus, and moderate to severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis.

Meaning Among patients undergoing TAVR, risk factors for subsequent endocarditis were identified; mortality associated with endocarditis was high.

Methods

Study Population and Clinical Data

The Infectious Endocarditis after TAVR International Registry retrospectively collected data from patients diagnosed with definite infective endocarditis after TAVR from a total of 47 sites from Europe, North America, and South America between June 2005 and October 2015 (**Figure 1**). Sites were contacted by the senior investigator (J.R.C.) and invited to participate in the registry. Patients were included in the registry irrespective of the valve affected. A dedicated case report form was used for data collection that included baseline and periprocedural TAVR features, as well as infective endocarditis characteristics and in-hospital and follow-up outcomes. Only patients with definite infective endocarditis were included, and only the first episode of infective endocarditis recorded for an individual patient was used in the analysis. In addition to the infective endocarditis data, all centers were asked to provide the total number of patients who had undergone TAVR but did not had infective endocarditis and had at least 1 year of follow-up. A total of 31 centers provided individual data on baseline, procedural, and follow-up features from the entire TAVR population. All patients gave written informed consent before the procedure(s), and all studies were performed in accordance with the local ethics committee of each center. Local institutional review boards waived the informed consent for the study due to its retrospective and anonymous nature. Data on 118 patients (47%) included in the present study have been reported in prior studies.[3,4,8,11]

Definitions

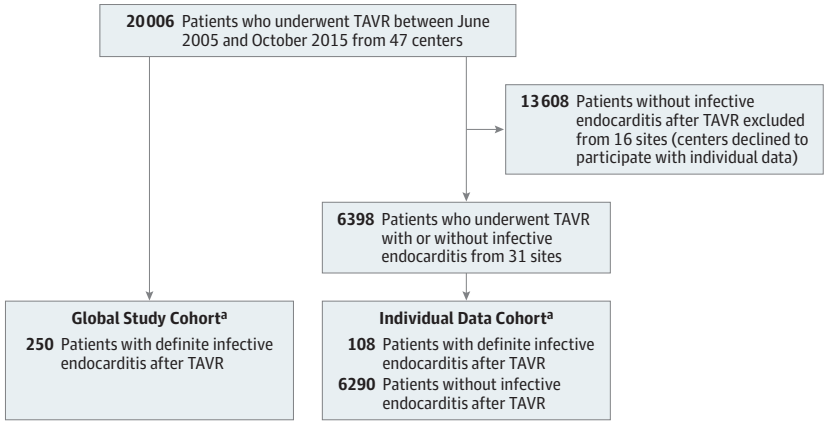
The definition of definite infective endocarditis was based on the modified Duke criteria.[12] Early infective endocarditis was defined as any infective endocarditis occurring within 12 months following the TAVR procedure.[1] Health care-associated endocarditis was defined by a positive blood culture obtained from a patient at the time of hospital admission or within 48 hours if the patient fulfilled any of the following criteria[13]: (1) received intravenous therapy at home or received wound care or specialized nursing care in the 30 days before the bloodstream infection; (2) attended a hospital or hemodialysis clinic or received chemotherapy in the 30 days before the bloodstream infection; (3) was hospitalized in an acute care hospital for 2 or more days in the 90 days before the bloodstream infection; or (4) resided in a nursing home or long-term care facility. Clinical events were defined according to the Valve Academic Research Consortium-2 criteria.[14] Periannular complication was defined as the presence of an intracardiac abscess, pseudoaneurysm, or fistula by transthoracic or transesophageal echocardiography. Other systemic embolization was defined as embolism to any major arterial vessel, excluding stroke. Persistent bacteriemia was defined as previously reported.[12] Perioperative mortality risk was defined according to the logistic EuroSCORE,[15] which includes the following variables: age, sex, chronic obstructive pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, renal failure, active endocarditis, critical preoperative state, unstable angina, left ventricle function, recent myocardial infarction, pulmonary hypertension, emergency surgery, surgery other than isolated coronary artery bypass graft, surgery on thoracic aorta, and postinfarct septal rupture.

Statistical Analysis

Continuous variables are presented as mean (SD) or median (interquartile range [IQR]) and categorical variables as percentages. Comparison between groups was performed using the *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact test for categorical variables. The Kaplan-Meier method was used to estimate the 2-year mortality rate.

The factors associated with in-hospital death after index infective endocarditis were assessed in the global study cohort. A multivariable logistic regression model was constructed. The candidate variables are presented in eAppendix 1 in the Supplement. Variables exhibiting a *P* value<.10 in

Figure 1. Flowchart of the Study Cohort



[a] Patients from the individual data cohort were selected among 31 centers that provided individual data. The 108 patients with definite infective endocarditis after transcatheter aortic valve replacement (TAVR) who were included in the Individual Data Cohort were also part of the Global Study Cohort.

the bivariable analysis were included in the multivariable model (Logistic EuroSCORE [per 1% increase], stroke, heart failure, and renal failure all during infective endocarditis hospitalization, and *Staphylococcus aureus* endocarditis). The model fit was evaluated with the area under the receiver operating characteristic curve.

The factors associated with infective endocarditis after TAVR were assessed from a subsample of centers that provided individual data from all patients who had undergone TAVR irrespective of the occurrence of infective endocarditis. A multivariable Cox proportional hazard model was constructed. Event times were measured from the date of TAVR to the date of diagnosis of infective endocarditis. The candidates variables are presented in eAppendix 1 in the Supplement. Variables exhibiting a P value <.10 in the bivariable analysis were included in the multivariable model (age [per 1-year increase], sex, diabetes mellitus, chronic renal failure, chronic pulmonary disease, orotracheal intubation, moderate to severe residual aortic regurgitation). The model was checked for violation of the proportional hazards assumption by assessing log-minus-log survival plots and scales Schoenfeld residuals. The validation was assessed by calculating the Harrell C concordance coefficient.

For bivariable analysis, patients with missing data for the covariate of interest were excluded. Missing data for each covariate included in the models are presented in eAppendix 2 in the Supplement. Missing data were assumed to be missing at random and were dealt with through the multivariable imputation using chained equations. The χ^2 test of missing completely at random was used to evaluate whether significant differences existed between the means of different missing-value patterns. The variables used to predict missing values were selected on a clinical basis. Ten imputed data sets for each model were created. To evaluate the potential statistical effect of clusters (sites and countries) a sensitivity analysis was performed comparing the multilevel models (patients nested within centers and centers within countries) estimates with the logistic regression and the Cox proportional hazard model estimates before imputation. The fixed-effects models were selected based on the similarity of the estimations, the loss of statistical power associated with the cluster size variability, and the limited number of patients per center. The multivariable association model covariates were summarized by reporting odds ratios (ORs) or hazard ratios (HRs) with approximate 95% CIs. A 2-sided $P < .05$ was considered statistically significant. Data analyses were performed using version 13.0 of the STATA statistical software (StataCorp LP).

Results

Study Global Cohort

Definite infective endocarditis was diagnosed in 250 of 20 006 patients after having undergone TAVR (incidence, 1.1% per person-year; 95% CI, 1.1%-1.4%). The median time between TAVR and the first symptoms was 5.3 months (IQR, 1.5-13.4 months). Early infective endocarditis occurred in 178 patients (71.2%; 95% CI, 65.6%-76.8%) for an incidence of 0.9% (95% CI, 0.77%-1.03%), including 72 patients (28.8%; 95% CI, 23.2%-34.4%) diagnosed within 2 months of the procedure. The baseline and periprocedural characteristics of the study population are shown in **Table 1**.

Factors Associated With Infective Endocarditis

The factors associated with infective endocarditis after TAVR were evaluated in a subset of 6398 patients (individual data available from 31 centers, including 6290 patients without and 108 patients with infective endocarditis). The baseline clinical and periprocedural characteristics according to the occurrence of infective endocarditis are shown in eTable 1 in the Supplement. Patients with infective endocarditis had a mean age of 78.9 years (95% CI, 77.6 to 80.2) vs 81.8 years (95% CI, 81.6 to 82.0; difference, −2.8 years; 95% CI, −4.2 to −1.4 years; $P < .001$). A total of 67 with endocarditis (62.0%) vs 3016 (49.7%) without were men (difference, 12.3%; 95% CI, 2.8% to 21.0%; $P = .01$), 45 (41.7%) vs 1577 (30.0%) had diabetes mellitus (difference, 11.6%, 95% CI, 2.7% to 21.1%; $P < .009$), and 39 (36.1%) vs 1439 (25.2%) had chronic pulmonary disease (difference,

Table 1. Baseline Clinical and Procedural Characteristics of Patients With Infectious Endocarditis Following Transcatheter Aortic Valve Replacement in the Global Study Cohort

	No. (%) of Patients (N = 250)
Baseline characteristics	
Age, median (IQR), y	80 (59-91)
Men	159 (63.6)
Diabetes mellitus	97 (38.8)
Chronic renal failure	117 (46.8)
COPD	78 (31.2)
Atrial fibrillation	97 (38.8)
Previous stroke	31 (12.4)
Previous infectious endocarditis	3 (1.2)
Previous valve surgery	29 (11.7)
Logistic EuroSCORE, median (IQR), %[a,b]	17.9 (10-28)
Mean transaortic gradient, mean (SD), mm Hg	45 (17)
Left ventricular ejection fraction, mean (SD), %	53 (13.9)
Aortic valve area, mean (SD), cm^2	0.72 (0.22)
Procedural characteristics	
Antibiotic prophylaxis	236 (94.4)
β-Lactam alone	195 (78.0)
Vancomycin alone	15 (6.0)
Valve implant site	
Catheterization laboratory	107 (42.8)
Operating or hybrid operating room	143 (57.2)
Type of valve	
Self-expandable valve[c]	119 (47.6)
Balloon-expandable valve[d]	131 (52.4)
Approach	
Transfemoral	208 (83.2)
Transapical	31 (12.4)
Transaortic	8 (3.2)
Other	3 (1.2)
Orotracheal intubation	137 (54.8)
In-hospital (TAVR) outcomes	
Device success[e]	204 (81.6)
Mean residual transaortic gradient, mean (SD), mm Hg	12 (7)
Aortic regurgitation (≥moderate)	39 (15.2)
Stroke	12 (4.8)
Major vascular complication	25 (10.0)
Major or life-threatening bleeding	29 (11.6)
Acute kidney injury	33 (13.2)
Permanent pacemaker implant	53 (21.2)
Length of hospital stay, median (IQR), d	9 (7-15)

Abbreviations: COPD, chronic obstructive pulmonary disease; TAVR, transcatheter aortic valve replacement.

[a] Information for the logistic EuroSCORE was available for 220 patients (88%).

[b] Range of score is 0.88% to 100%, a higher score indicates a worse prognosis.

[c] CoreValve system in 46% (115 of 250) of cases.

[d] Edwards valve in 52% (130 of 250) of cases.

[e] According to Valve Academic Research Consortium 2 definition.

10.9%; 95% CI, 2.4% to 20.4%; P = .01). The percentage of patients who received a self-expandable valve was not significantly different between groups with 38.9% (95% CI, 29.7% to 48.1%) with and 43.5% (95% CI, 41.5% to 45.4%) without infective endocarditis (difference, −4.6%; 95% CI, −13.5% to 4.8%; P = .34).

Forty-four patients (59.3%) with vs 2347 (48.1%) without infective endocarditis had general anesthesia with orotracheal intubation during the TAVR (difference, 11.1%; 95% CI, 1.6% to 20.0%; P = .02) and 22 (22.4%) with vs 770 (14.7%) without infective endocarditis experienced residual moderate or severe aortic regurgitation after TAVR (difference, 7.8%; 95% CI, 0.6% to 17.0%; P = .03). Patients who received a self-expandable valve were younger than those who received a balloon-expandable valve (81.4 years vs 81.9 years; difference, −0.5 years; 95% CI, −0.9 to −0.1; P = .01]. There were no other significant differences in baseline or procedural characteristics and outcomes according to the type of valve. Performing the TAVR procedure in a catheterization laboratory (vs operating room or hybrid operating room, which has full catheterization laboratory hemodynamic capability) was not more frequent among patients who had infective endocarditis (80.6%; 95% CI, 73.0% to 88.0% among patients with vs 83.2%; 95% CI, 82.2% to 84.1% without infective endocarditis; difference, 2.6%; 95% CI, −3.8% to 11.1%; P = .47). In multivariable analyses, age (HR, 0.97; 95% CI, 0.94 to 0.99), male sex (HR, 1.69; 95% CI, 1.13 to 2.52), history of diabetes mellitus (HR, 1.52; 95% CI, 1.02 to 2.29), and the presence of a residual moderate or severe aortic regurgitation (HR, 2.05; 95% CI, 1.28 to 3.28) were associated with increased risk of infective endocarditis during follow-up (**Table 2**).

Clinical and Echocardiographic Characteristics

Clinical characteristics, management, and outcomes of infective endocarditis after TAVR are shown in **Table 3**. The most common symptoms at presentation were fever (80.4%; 95% CI, 75.5%-85.3%) and acute heart failure (40.0%; 95% CI, 39.3%-51.7%). A possible source of bacteremia was identified in 30.4% of patients (95% CI, 43.8%-56.2%). The most frequent source of bacteremia was a soft tissue infection or presumed intravascular source, which was identified in 26 patients (10.4%, 95% CI, 6.6%-14.2%). Health care-associated infective endocarditis was present in 132 patients (52.8%; 95% CI, 46.6%-59.0%). Among the remaining 47.2% of patients (95% CI, 41.0%-53.4%) without a health care-associated infection, 74.6% (95% CI, 69.2%-80.0%) did not have any identifiable possible source of bacteremia.

Enterococcus species (24.6%; 95% CI, 19.1% to 30.1%) and *S aureus* (23.8%; 95% CI, 17.9% to 28.7%) were the most common causative organisms, followed by coagulase-negative staphylococci (16.8%; 95% CI, 12.0% to 21.6%). In patients with early infective endocarditis, *Enterococcus* species was the most frequent causative organism (24.7%; 95% CI, 19.3% to 30.1%), followed by *S aureus* (21.9%; 95% CI, 16.8% to 27.0%). Among patients who underwent the procedure in the catheterization laboratory, 24% were infected with the *Enterococcus* species (95% CI, 16.3% to 33.1%) vs 29.8% of

Table 2. Factors Associated With Infectious Endocarditis Following Transcatheter Aortic Valve Replacement in the Individual Data Cohort Study

	Infective Endocarditis (n = 108)	Noninfective Endocarditis (n = 6290)	Patient-Years of Follow-up	Infective Endocarditis Rate per 1000 Patients (95% CI), y	Adjusted Hazard Ratio (95% CI)[a,b]	*P* Value
Age, median (IQR), y[c]	80 (74-83)	83 (78-87)				
Per 1-y increase					0.97 (0.94-0.99)	.003
Sex						
Women	41	3054	4557	8.3 (6.1 to 11.5)	1 [Reference]	.01
Men	67	3016	4592	13.5 (10.5 to 17.3)	1.69 (1.13-2.52)	
Diabetes mellitus						
No	63	3675	5947	9.7 (7.5 to 12.6)	1 [Reference]	.04
Yes	45	1577	2463	17.0 (12.6 to 23.0)	1.52 (1.02-2.29)	
Chronic pulmonary disease						
No	69	4270	6724	9.8 (7.7 to 12.5)	1 [Reference]	.16
Yes	39	1439	2346	14.5 (10.3 to 20.3)	1.35 (0.89-2.04)	
Orotracheal Intubation						
No	44	2527	3639	11.5 (0.8-15.6)	1 [Reference]	.22
Yes	64	2347	3565	16.3 (12.6-21.0)	1.28 (0.68-1.93)	
Residual aortic regurgitation						
No or mild	76	4484	7593	9.3 (7.4 to 11.8)	1 [Reference]	.003
Moderate or severe	22	770	1289	16.3 (10.6 to 25.0)	2.05 (1.28-3.28)	

[a] For the Cox proportional hazard model, patients with missing data were included thought the use of multivariable imputation using chained equations.

[b] Multivariable-adjusted model including age (per 1-y increase), sex (men-women), diabetes mellitus (yes-no), chronic renal failure (glomerular filtration rate, <60 mL/min/1.73 m^2), orotracheal intubation (yes-no), chronic pulmonary disease (yes-no), moderate to severe residual aortic regurgitation (yes-no).

[c] Information was available for 104 patients in the infective endocarditis group and 6074 patients in the noninfective endocarditis group.

patients who underwent the procedure in an operating room or hybrid operating room (95% CI, 21.8% to 37.5%; difference, 5.0%; 95% CI, −6.7% to 16.4%; *P* = .30). Among those infected with *S aureus*, 24.7% (95% CI, 16.3% to 33.1%) underwent the procedure in the catheterization laboratory vs 27.5% (95% CI, 19.8% to 35.1%) who underwent the procedure in the operating room or hybrid room (difference, 2.5%; 95% CI, −8.9% to 13.5%; *P* = .64). The causative organisms of infective endocarditis for the entire study population are shown in eTable 2 in the Supplement.

Echocardiography revealed the presence of vegetations in 165 patients (67.6%; 95% CI, 61.7%-73.5%), with a largest mean (SD) size of 10.7 mm (7.5 mm). Vegetations were anchored to the stent frame among 18.2% (30 of 165) of patients (95% CI, 12.3%-24.1%) or anchored to the leaflets of the transcatheter valve among 47.9% (79 of 165) of patients (95% CI, 40.3%-55.5%) (eFigure 1 in the Supplement). Of the patients who received a self-expandable valve, 26.2% (21 of 80) had vegetations within the stent frame vs 10.6% (9 of 85) who received balloon-expandable valves (difference, 15.6%; 95% CI, 3.8%-27.3%; *P* = .01), whereas 58.8% (50 of 85) of patients who received a balloon-expandable valve had valve-leaflet level vegetation vs 36.2% (29 of 80) patients who had received self-expandable valves (difference, 22.6%; 95% CI, 7.3%-26.2%; *P* = .02). Concomitant mitral valve involvement was found in 50 patients (20.0%; 95% CI, 15.0%-25.0%), tricuspid in 11 (4.4%; 95% CI, 1.9%-6.9%), and in pacemaker devices of 15 (6.0%; 95% CI, 3.1%-8.9%). New moderate to severe mitral regurgitation was observed in 34 patients (13.9%; 95% CI, 9.6%-18.2%), and new moderate to severe aortic regurgitation was observed in 24 patients (9.8%; 95% CI, 6.1-13.5). Periannular complications were diagnosed in 44 patients (18.0%; 95% CI, 13.2%-22.8%), including the presence of abscess (15.6%; 95% CI, 11.1%-20.1%), fistulas (1.6%; 95% CI, 0.4%-3.2%), and pseudoaneurysms (0.4%; 95% CI, 0%-1.2%) (eFigure 2 in the Supplement).

Management and Outcomes

Complications during infective endocarditis hospitalization were observed in 160 patients (64.0%; 95% CI, 58.1%-70.0%) and are summarized in Table 3. A total of 203 patients (81.2%; 95% CI, 76.4%-86.0%) had at least 1 indication for surgery. Surgery during the index hospitalization was performed in 37 patients (14.8%; 95% CI, 10.4%-19.2%), including surgical transcatheter valve explantation in 27 patients (10.8%; 95% CI, 6.9%-14.6%). Nonsurgical interventional treatment was performed in 10 patients (4%; 95% CI, 1.6%-6.4%), including TAVR valve-in-valve implant (1.2%; 95% CI, 0%-2.5%) and isolated pacemaker extraction (2.8%; 95% CI, 0.8%-4.8%). The remaining 205 patients (82.0%; 95% CI, 77.2%-86.8%) were treated with antibiotic therapy alone. β-Lactam antibiotics alone were used in 38 patients (15.2%; 95% CI, 10.7%-19.6%), and in combination with other antibiotics in 126 patients (50.4%; 95% CI, 44.2%-56.6%). Vancomycin was used alone or in combination with other antibiotics in 53 patients (21.2%; 95% CI, 16.1%-26.3%).

Table 3. Clinical Characteristics, Management, and Outcomes of Patients With Infectious Endocarditis Post-Transcatheter Aortic Valve Replacement (Global Study Cohort)[a]

	Patients (n = 250)
Time from TAVR, median (IQR), mo[b]	5.3 (1.5-13.4)
Early post-TAVR endocarditis (<1 y)	178 (71.2)
Initial symptoms	
Fever	201 (80.4)
Acute heart failure	100 (40.0)
Neurological	42 (16.8)
Cutaneous	8 (3.2)
Systemic embolism	32 (12.8)
Health care-associated infection	132 (52.8)
Exposure to sources of bacteremia before infective endocarditis	
Unknown	174 (69.6)
Presumed intravascular source/ Soft tissue infection	26 (10.4)
Gastrointestinal	17 (6.8)
Urologic	16 (6.4)
Odonatological	9 (3.6)
Pacemaker implant	8 (3.2)
Antibiotic prophylaxis	125 (50)
Causative organism[c]	
Enterococcus species	57/232 (24.6)
Staphylococcus aureus	54/232 (23.3)
Coagulase-negative *Staphylococcus*	41/232 (16.8)
Viridans streptococci	16/232 (6.9)
Culture negative	12/232 (5.2)
Echocardiographic findings, No./total (%)[d]	
Vegetations	165/244 (67.6)
Transcatheter aortic valve leaflets	79/165 (47.9)
Transcatheter aortic valve stent	30/165 (18.2)
Mitral	41/165 (24.8)
Pacemaker lead	7/165 (4.8)
Tricuspid	7/165 (4.8)
Periannular complication	44/244 (18.0)
New aortic regurgitation	24/244 (9.8)
New mitral regurgitation	34/244 (13.9)
Complications during infective endocarditis hospitalization, No./total (%)	
Any complication	160/238 (67.2)
Heart failure	87/238 (36.6)
Acute kidney injury	106/238 (44.5)
Septic shock	66/238 (27.7)
Stroke	25/238 (10.5)
Other systemic embolization	22/238 (9.2)
Persistent bacteremia	51/238 (21.4)
Management and in-hospital outcomes	
Surgery during infective endocarditis hospitalization	37 (14.8)
Surgical transcatheter valve explantation	27 (10.8)
Surgical treatment without valve explantation	10 (4.0)
Transcatheter valve-in-valve procedure	3 (1.2)
Isolated pacemaker extraction	7 (2.8)
In-hospital death	90 (36.0)

(continued)

Table 3. Clinical Characteristics, Management, and Outcomes of Patients With Infectious Endocarditis Post-Transcatheter Aortic Valve Replacement (Global Study Cohort)[a] (continued)

	Patients (n = 250)
Follow-up outcomes[e]	
Follow-up time after infective endocarditis, median (IQR), mo	10.5 (3.0-20.8)
Total person-years	171.5
Recurrent infective endocarditis, No./total (%)	15/160 (9.4)
Death at follow-up, No./total (%)	50/160 (31.5)
2-y mortality rate, (95% CI), %[e]	66.7 (59.0 to 74.2)

Abbreviation: TAVR Transcatheter valve aortic replacement.

[a] Data are expressed as No. (%) of patients unless otherwise indicated.

[b] Information for the time from TAVR to infective endocarditis was available for 245 patients (98%).

[c] Information for causative organism was available for 232 patients (92.8%).

[d] Echocardiographic information for the infective endocarditis episode was available for 244 patients (97.6%).

[e] Follow-up time was not available for 3 patients (1.2%).

In-hospital death occurred in 90 cases (36%; 95% CI, 30.0% to 41.9%). Patients who died in the hospital were more likely to have a higher logistic EuroSCORE (23.1%; 95% CI, 11.2% to 17.0% vs 18.6%; 95% CI, 16.7% to 20.5%; difference, 4.4%; 95% CI, 0.9 to 8.0; OR, 1.03 per 1% increase; 95% CI, 1.00 to 1.05; P = .02), have heart failure at admission (59.3%; 95% CI, 49.1 to 69.4% vs 23.7%; 95% CI, 17.1% to 30.3%; difference, 35.5%; 95% CI, 22.7% to 47.1%; OR, 3.36; 95% CI, 1.74 to 6.45; P < .001), and have acute kidney injury (67.4%; 95% CI, 57.7% to 77.1% vs 31.6%; 24.4% to 38.8%; difference 35.9%; 95% CI, 22.8% to 47.2%; OR, 2.70; 95% CI, 1.42 to 5.11; P = .002) (**Table 4**). The baseline clinical and periprocedural characteristics according to in-hospital death are shown in eTable 3 in the Supplement. There were no significant differences between the type of valve regarding in-hospital death (34.4%; 95% CI, 25.9% to 42.9%, for self-expandable valve vs 37.4%; 95% CI, 29.1% to 45.7%, for balloon-expandable valve; P = .63; difference, 2.9%; 95% CI, −8.9% to 14.6%). Surgery during infective endocarditis hospitalization was not associated with a reduced risk of in-hospital death (29.7%; 95% CI, 15.0% to 44.4% for surgery vs 37.1%; 95% CI, 30.6% to 43.6% for no surgery; difference, −7.4%; 95% CI, −21.3% to 0.8%; OR, 0.72; 95% CI, 0.33 to 1.53; P = .39).

The median follow-up period of the 160 patients who survived the in-hospital treatment period was 10.5 months (IQR, 3-21). A second episode of infective endocarditis was identified in 15 patients (9.4% of those patients who survived the initial infective endocarditis episode). A total of 50 patients died during the total follow-up period leading to a 2-year mortality of 66.7% (95% CI, 59.0%-74.2%; 132 deaths; 115 survivors). The distribution of cause of death during follow-up included, infection-related complications (n = 14), cardiovascular events (n = 5), cancer (n = 3), renal failure (n = 2), major bleeding (n = 1), trauma (n = 1), incarcerated ventral hernia (n = 1), unexpected or sudden death (n = 8), and unknown reasons (n = 15). The Kaplan-Meier survival curve at the 24-month follow-up for the population with infective endocarditis after

Table 4. Factors Associated With In-Hospital Death in Patients With Infectious Endocarditis Following Transcatheter Aortic Valve Replacement (Global Study Cohort)

	No In-Hospital Death (n = 160)	In-Hospital Death (n = 90)	Adjusted Odds Ratio (95% CI)[a,b]	*P* value
Logistic EuroSCORE[c]	18.6 (12.2)	23.1 (14.1)		
Per 1% increase			1.03 (1.00-1.05)	.02
Stroke during infective endocarditis hospitalization				
No	141	72	1 [Reference]	.10
Yes	11	14	2.29 (0.85-6.16)	
Heart failure during infective endocarditis hospitalization				
No	116	35	1 [Reference]	<.001
Yes	36	51	3.36 (1.74-6.45)	
Renal failure during infective endocarditis hospitalization				
No	104	28	1 [Reference]	.002
Yes	48	58	2.70 (1.42-5.11)	
Staphylococcus aureus endocarditis				
No	117	54	1 [Reference]	.10
Yes	31	30	1.76 (0.90-3.44)	

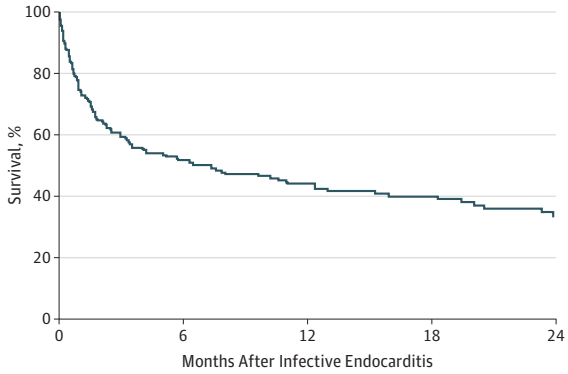
[a] For the Logistic Regression Model, patients with missing data were included thought the use of multivariable imputation using chained equations.

[b] Multivariable-adjusted model including logistic EuroSCORE (per 1% increase), stroke during infective endocarditis hospitalization (no-yes), Heart failure during infective endocarditis hospitalization (no-yes), Renal failure during infective endocarditis hospitalization (no-yes), *S aureus* endocarditis (no-yes)

[c] Information was available for 136 patients in the non in-hospital death group and 84 patients in the in-hospital death group

TAVR is shown in **Figure 2**. The univariable and multivariable analyses for determining the factors associated with late mortality after infective endocarditis are shown in eTable 4 in the Supplement. The independent factors associated with late death were a higher logistic EuroSCORE (22.8%; 95% CI, 20.5%-25.1% vs 16.6%; 95% CI, 14.5%-18.7%; difference, 6.2% 95% CI, 2.7%-9.6%; hazard ratio (HR), 1.03 per 1% increase; 95% CI, 1.00-1.06) and heart failure during infective endocarditis hospitalization (78.1%; 95% CI, 69.5%-86.4%, for patients with heart failure vs 43.2%, 95% CI, 35.2%-51.2% for the patients without heart failure; difference, 34.9%; 95% CI, 22.2%-45.6%; HR, 2.32; 95% CI, 1.16-4.66; *P* = .02).

Figure 2. Survival Curve for Patients With Infective Endocarditis After Transcatheter Aortic Valve Replacement in the Global Study Cohort



Kaplan-Meier survival curve during the 24-month follow-up after infective endocarditis following transcatheter aortic valve replacement. Median follow-up of 10.5 months (interquartile range, 3-21 months). Follow-up time was not available for 3 patients.

Discussion

Prosthetic valve endocarditis has been recognized as the most severe form of infective endocarditis, occurring in 1% to 6% of patients with valve prostheses, accounting for 10% to 30% of all cases of infective endocarditis.[1] The rate of infective endocarditis after TAVR observed in the present study is similar to that reported for surgical prosthetic valve endocarditis,[1] therefore, supports the lack of reduction in the rate of prosthetic valve infective endocarditis after TAVR despite less invasive nature of TAVR compared with surgical valve replacement. This study confirms the high rate of morbidity and mortality of infective endocarditis after TAVR and provides novel information about the timing, causative organisms, and predictive factors of infective endocarditis in this particular population. This information may help the clinicians identify patients at higher risk and aid in implementing appropriate preventive measures.

Factors Associated With Infective Endocarditis

Although the median age of patients in the population was 80 years, patients who were younger were at increased risk of infective endocarditis after TAVR. There is no clear explanation for this finding. However, younger patients considered at high or prohibitive surgical risk may exhibit a higher comorbidity burden than their older counterparts. This may have been associated with an increased risk of infective endocarditis. Similarly, sex differences in comorbid conditions and outcomes in patients undergoing TAVR may partially explain the higher risk of infective endocarditis among male patients.[16] Prior studies have already found an association between diabetes and increased risk of infective endocarditis.[17]

Residual moderate or severe aortic regurgitation is associated with lower survival after TAVR.[18] Aortic regurgitation is associated with abnormal blood flow, turbulence, and

high-shear stress. This may predispose platelets and fibrin to deposit resulting in nonbacterial thrombotic endocarditis and vegetations.[19] These deleterious effects may play an important role on the occurrence and maintenance of device infection.[20] Also, a higher valve calcification, which has been associated with aortic regurgitation after TAVR, may also contribute to the higher risk of infective endocarditis.[21] These results suggest that a more aggressive approach by including antibiotic prophylaxis (as recommended by current guidelines). Reducing the risk of bacteremia by eradicating unnecessary procedures and reinforcing the preventive measures could be considered for patients with significant aortic regurgitation after TAVR. Other periprocedural TAVR features like transcatheter valve type or orotracheal intubation were found to be factors associated with infective endocarditis in prior smaller studies,[3] but these findings were not confirmed in the current study, which included a significantly larger series of patients.

Clinical, Microbiological, and Imaging Characteristics

The percentage of infective endocarditis within 60 days after TAVR observed in our study (29%) contrasts with the 14% reported by the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (PCS).[22] These differences may be secondary to both the higher-risk profile and the high burden of instrumentation in the TAVR population, suggesting the need for a more cautious approach by avoiding unnecessary invasive examinations and reinforcing the importance of maintaining aseptic conditions during any invasive procedure to reduce the exposure to possible sources of bacteremia.

In contrast to prior studies on prosthetic valve infective endocarditis,[22] enterococci were the most frequent causative microorganisms of infective endocarditis in the present study. The rates of *S aureus* and coagulase-negative staphylococci infection were similar to those previously reported.[22] Advanced age, chronic diseases, and aortic valve calcification have been associated with enterococcal infective endocarditis. This may partially explain the higher proportion of enterococcal infection in patients with TAVR than in their surgical prosthetic valve infective endocarditis counterparts. Also, the use of transfemoral access in TAVR (enterococci are a frequent groin contaminant) and the high rate of enterococci infective endocarditis within the 60 days following the procedure suggests the need for antibiotic prophylaxis before the procedure and careful infection control during and after the procedure. The high prevalence of enterococci infective endocarditis should be taken into consideration in the antibiotic selection while waiting for the blood culture results in patients with suspicion of infective endocarditis after TAVR. Also, the type of antibiotic prophylaxis in such patients may be further evaluated in view of the present findings. β-Lactam antibiotics were used as antibiotic prophylaxis during TAVR procedures in most patients, but their efficacy in preventing enterococci infections is limited; glycopeptides and aminoglycosides would seem a better option in such cases.[23]

The presence of vegetations is in accordance with a prior surgical prosthetic valve infective endocarditis series.[22] Interestingly, vegetations attached to the stent frame were found almost 3 times more frequently in patients who received a self-expandable valve than those treated with a balloon-expandable valve. The larger stent frame of self-expandable devices may partially explain such differences. Additionally, the involvement of pacemaker devices in some instances should be noted, particularly considering the high rate of pacemaker implantation after TAVR. These features, which are specific to transcatheter valves, should be taken into account when evaluating a patient with a clinical suspicion of infective endocarditis after TAVR.

Outcomes and Management

The presence of heart failure and acute kidney injury during an infective endocarditis episode and a higher surgical preprocedural risk were associated with increased in-hospital mortality, regardless of the use of surgical therapy. Heart failure was the strongest predictor of in-hospital mortality, confirming the significance of this complication in patients with infective endocarditis after TAVR. A higher logistic EuroSCORE was also associated with an increased risk of in-hospital death, which reflects the influence of comorbidities on outcome following infective endocarditis in this high-risk population. The 67% mortality at the 2-year follow-up in this study seems to be higher than that observed after prosthetic surgical valve endocarditis (27% to 61%).[24,25] Although this may be partially explained by the more advanced age and higher comorbidity burden of the TAVR population, this mortality rate seems higher than that observed 2 years after TAVR in patients at high surgical risk (22% in the US pivotal trial for the self-expanding valve[26] and 34% in the Placement of Aortic Transcatheter Valves [PARTNER] trial[27]). This highlights the poor prognosis of patients with infective endocarditis after TAVR.

Early surgery in patients with infective endocarditis and severe valve dysfunction or large vegetations reduces the risk of in-hospital death and embolic events.[28] In patients with prosthetic valve endocarditis, current guidelines recommend surgical intervention with debridement and valve replacement for patients with severe valve dysfunction, heart failure, cardiac abscesses, highly resistant organisms, or persistent bacteriemia.[1,2] Lalani et al[29] reported a valve surgery rate close to 50% in a contemporary cohort of patients with prosthetic valve endocarditis. This contrasts with the 10.8% rate of surgery with valve explantation observed in our study despite the very high rate (>80%) of patients with at least 1 indication for surgery according to current guidelines. This very low rate of valve surgery is likely secondary to the high or prohibitive surgical risk of such patients, in addition to the potential technical difficulties of removing a stent frame adherent to the aorta. However, and unlike prior studies, valve surgery was not associated with a mortality benefit in our study. Although this may be related to a selection bias and the high surgical risk of TAVR patients or to the limited number of patients who underwent valve explantation, further studies need to address the potential benefits of surgical therapy in this challenging group of patients.

Limitations

First, this was a retrospective registry. Although this may be less relevant regarding the description of the clinical

characteristics and outcomes, it represents an important limitation when evaluating the incidence of infective endocarditis, their associated factors, source of entry, and adequacy of preventive measures. Second, there was no external monitoring or event adjudication committee to verify the accuracy of the data reported by each center. Third, the influence of confounding factors other than those included in the multivariable models cannot be completely excluded.

Conclusions

Among patients undergoing TAVR, younger age, male sex, history of diabetes mellitus, and moderate to severe residual aortic regurgitation were significantly associated with an increased risk of infective endocarditis. Patients who developed endocarditis had a high rate of in-hospital mortality and a low rate of surgical valve explantation.

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