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Temporal Trends, Characteristics, and Outcomes of Infective Endocarditis After Transcatheter Aortic Valve Replacement

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Background. Procedural improvements combined with the contemporary clinical profile of patients undergoing transcatheter aortic valve replacement (TAVR) may have influenced the incidence and outcomes of infective endocarditis (IE) following TAVR. We aimed to determine the temporal trends, characteristics, and outcomes of IE post-TAVR.

Methods. Observational study including 552 patients presenting definite IE post-TAVR. Patients were divided in 2 groups according to the timing of TAVR (historical cohort [HC]: before 2014; contemporary cohort [CC]: after 2014).

Results. Overall incidence rates of IE were similar in both cohorts (CC vs HC: 5.45 vs 6.52 per 1000 person-years; $P = .12$), but the rate of early IE was lower in the CC (2.29‰ vs 4.89‰, $P < .001$). Enterococci were the most frequent microorganism. Most patients presented complicated IE (CC: 67.7%; HC: 69.6%; $P = .66$), but the rate of surgical treatment remained low (CC: 20.7%; HC: 17.3%; $P = .32$). The CC exhibited lower rates of in-hospital acute kidney injury (35.1% vs 44.6%; $P = .036$) and in-hospital (26.6% vs 36.4%; $P = .016$) and 1-year (37.8% vs 53.5%; $P < .001$) mortality. Higher logistic EuroScore, *Staphylococcus aureus* etiology, and complications (stroke, heart failure, and acute renal failure) were associated with in-hospital mortality in multivariable analyses ($P < .05$ for all).

Conclusions. Although overall IE incidence has remained stable, the incidence of early IE has declined in recent years. The microorganism, high rate of complications, and very low rate of surgical treatment remained similar. In-hospital and 1-year mortality rates were high but progressively decreased over time.

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Infective endocarditis (IE) following transcatheter aortic valve replacement (TAVR) is a rare but life-threatening complication. The incidence of IE post-TAVR ranges between 0.9% and 3.1% at 1-year follow-up, similar to that reported following surgical aortic valve replacement [1, 2]. Transcatheter aortic valve replacement has revolutionized the treatment of severe aortic stenosis and is currently expanding towards the treatment of younger patients with a lower surgical risk [3]. Thus, the number of patients at risk of developing IE after TAVR is growing exponentially. Infective endocarditis post-TAVR is associated with high in-hospital mortality and patients who survive the index IE episode showed a poor long-term prognosis, with nearly two-thirds dying at 5-year follow-up [4–6].

In the last few years, there has been an increasing interest in simplifying and reducing invasive healthcare procedures in TAVR. The potential benefits of both device iterations and procedural changes (eg, no general anesthesia) are a shorter hospital length of stay, earlier patient ambulation, lower risk for nosocomial infections, and lower in-hospital mortality [7, 8]. However, it remains unknown whether such improvements combined with the contemporary clinical profile of patients undergoing TAVR have impacted the incidence and outcomes of IE episodes in this particular population. Thus, the objectives of this study including a large cohort of patients with definite IE after TAVR were to determine the temporal trends regarding the incidence, clinical characteristics, management, and outcomes of IE episodes post-TAVR.

METHODS

Data from the Infectious Endocarditis After TAVR International Registry were used for this study. Details about the design of this retrospective, multicenter, international registry have been published previously [4]. Briefly, the registry collected data from 552 patients with definite IE after TAVR from 56 TAVR centers in 10 countries across Europe, North America, and South America between June 2005 and May 2020.

Patient Selection and Data Collection

Patients were retrospectively identified by each center according to the modified Duke criteria. Only patients with definite IE were included, irrespective of the structure affected (native/prosthetic valve or implantable cardiac device). Also, only the first episode of IE recorded for an individual patient was included in the analysis. A dedicated database was used in all sites for data collection including baseline and periprocedural TAVR features, IE characteristics, and in-hospital and follow-up outcomes. Based on the TAVR date, the global cohort was divided into 2 cohorts of patients. The division date (31 December 2013) was prespecified on the basis of the following criteria: (1) to reflect a new era for TAVR with important platform iterations (second-generation valves) and procedural changes that may have influenced IE epidemiology and (2) to divide the entire cohort into 2 similar (numerically) groups of patients. A total of 285 patients were included in the historical cohort (HC; June 2005 to December 2013) and 263 patients in the contemporary cohort (CC; January 2014 to May 2020). Four patients were excluded from the final analysis because of missing data of TAVR date. Also, participating sites were asked to provide data on the total number of TAVR procedures (overall and according to TAVR time) and individual data concerning TAVR patients' follow-up. The flowchart of the study population is depicted in Figure 1. Data from up to 250 patients (45%) included in the present study have been reported in a prior study (203 and 47 patients corresponding to the HC and CC, respectively) [4].

Definitions

The definition of definite IE was based on the modified Duke criteria [9]. Clinical endpoints were defined according to the Valve Academic Research Consortium-2 criteria [10]. Perioperative mortality risk was defined according to the logistic EuroScore [11]. Transcatheter aortic valve type was divided into 2 groups: balloon-expandable valves and self- or mechanically expandable valves. Infective endocarditis with no TAVR platform affection was defined as any IE episode not involving the TAVR prosthesis. Early prosthetic valve endocarditis (PVE) was defined as occurring within 60 days of TAVR [12, 13]. Healthcare-associated IE was defined using Friedman et al [14] criteria. Persistent bacteremia was defined as bacteremia despite appropriate antibiotic therapy for more than 7 days. Periannular complications and other systemic embolization were defined as previously reported [4].

Statistical Analysis

Continuous variables were expressed as means ± standard deviations or medians (interquartile ranges [IQRs]) depending on the variable distribution, which was assessed using the Kolmorogov-Smirnov test. Incidence rates and incidence rate ratios were calculated using a subsample of centers that provided individual data from all of the patients undergoing TAVR, irrespective of the occurrence of IE. Categorical variables were expressed as numbers (%). Group comparison was analyzed using the Student's *t* test or Wilcoxon rank-sum test for continuous variables and chi-square or Fisher's exact test for categorical variables. A multivariable Cox proportional hazards model was performed to determine the factors independently associated with in-hospital mortality. The variables considered a priori to contribute to in-hospital mortality and with a *P* value less than .10 in the bivariate analysis were included in the model.

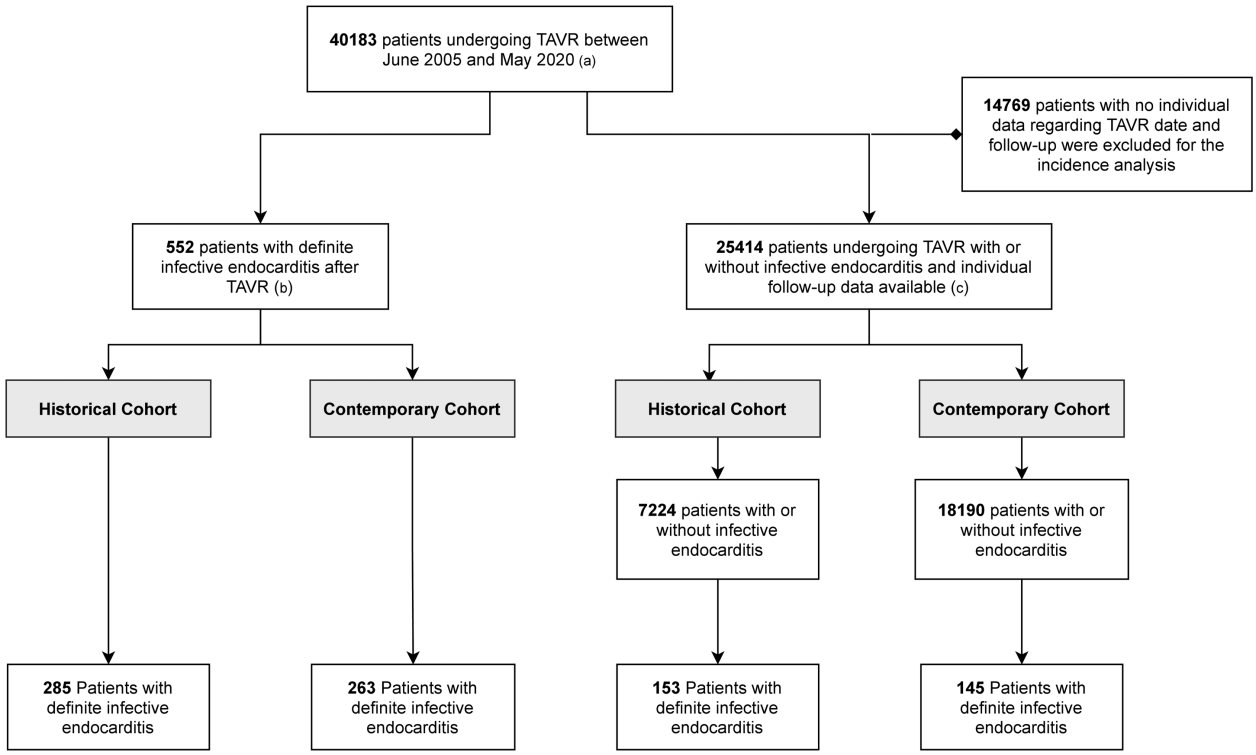

Figure 1. Flowchart of the study population. *A*, Forty-three centers reporting data on the total number of TAVR procedures, overall and according to the occurrence of infective endocarditis post-TAVR. *B*, Time of TAVR was missing in 4 patients. *C*, Thirty-two centers reporting individual data regarding TAVR patients' follow-up. Patients with definite infective endocarditis to determine the incidence estimation were also part of the overall study cohort. Abbreviation: TAVR, transcatheter aortic valve replacement.

The model was built by backward stepwise (likelihood ratio) selection. The proportional hazards assumption was tested by assessing log-minus-log survival plots and scaled Schoenfeld residuals. The Kaplan-Meier method was used to provide survival estimates with differences assessed by the log-rank test. Event times were measured from the date of initial IE symptoms to the date of death or last follow-up. A 2-sided *P* value of less than .05 was considered statistically significant. Data analyses were performed using the Stata software (StataCorp, College Station, TX, USA) and Prism (GraphPad Software, San Diego, CA, USA).

RESULTS

Baseline and Procedural Characteristics

The main baseline and procedural characteristics of the study population, overall and according to the timing of the TAVR procedure (CC and HC groups), are shown in Table 1. Definite IE was diagnosed in 552 patients following TAVR. The median follow-up of the entire TAVR population was 16.2 months (IQR, 10.0–36.2 months). The median age of the patients was 80.7 years (IQR, 74.6–85.1 years), with 61.2% men (95% confidence interval [CI], 57.2–65.3%) and a median logistic EuroScore of 14.5% (IQR, 8.6–24.2%). Most procedures (87.9%; 95% CI, 85.1–90.6%) were performed through transfemoral approach.

Infective endocarditis following TAVR was diagnosed in 285 patients in the HC (incidence rate of 6.52 [95% CI, 5.54–7.67] per 1000 patient-years) and 263 patients in the CC (incidence rate of 5.45 [95% CI, 4.65–6.38] per 1000 patient-years). There was no significant temporal variation regarding the overall IE incidence between both cohorts (incidence rate ratio of .84 [95% CI, .66–1.05]; $P = .123$), but the incidence of early IE (within 60 days of the procedure) was significantly lower in the CC (incidence rate in HC vs CC: 4.89 vs 2.29 per 1000 patients; difference, 2.7; 95% CI, 1.0–4.2; $P < .001$). Patients in the CC were older (HC vs CC: 79.3 vs 81.7 years; difference, −2.4 years; $P < .01$) and exhibited a lower risk profile for TAVR as determined by the logistic EuroScore (HC vs CC:16.1% vs 12.6%; difference, 3.5%; $P = .03$). Transcatheter aortic valve replacement procedures in the CC were more frequently performed through transfemoral approach (HC vs CC: 83.9% vs 92.4%; difference, −8.5%; 95% CI, −13.9% to −3.2%; $P < .001$), without general anesthesia/endotracheal intubation (HC vs CC: 54.0% vs 31.2%; difference, 22.9%; 95% CI, 14.8% to 30.9%; P<0.001)), but there were no differences between cohorts regarding transcatheter valve type. A significant reduction in the use of vancomycin for antibiotic prophylaxis was observed in the CC (HC vs CC: 6.3% vs 1.5%; difference, 4.8%; 95% CI, 1.6–8.0%; $P = .012$). The median hospitalization length of stay was much shorter in the

Table 1. Baseline Characteristics, Procedural Details, and In-Hospital Transcatheter Aortic Valve Replacement (TAVR) Outcomes, Overall and According to the Time of TAVR (Historical vs Contemporary Cohort)

	Overall (N = 552)[a]	Historical Cohort (n = 285)	Contemporary Cohort (n = 263)	Unadjusted *P* Value
Baseline characteristics				
Age, median (IQR), years	80.7 (74.6–85.1)	79.3 (73.9–84.1)	81.7 (75.6–85.7)	.010
Female, n (%)	214 (38.8)	118 (41.4)	94 (35.7)	.174
Body mass index, median (IQR), kg/m^2	27.0 (24–30.8)	27.1 (24.2–31.1)	26.8 (24–31)	.616
Diabetes mellitus, n (%)	202 (36.6)	105 (36.8)	96 (36.5)	.934
COPD, n (%)	150 (27.2)	83 (29.1)	67 (25.5)	.339
Atrial fibrillation, n (%)	232 (42.0)	105 (36.8)	126 (47.9)	.010
Chronic renal failure, n (%)	216 (39.1)	121 (42.5)	94 (35.7)	.163
Previous stroke, n (%)	75 (13.6)	35 (12.3)	40 (15.2)	.319
Previous valve surgery, n (%)	64 (11.6)	28 (9.8)	36 (13.7)	.159
Previous infectious endocarditis, n (%)	9 (1.6)	3 (1.1)	6 (2.3)	.324
Logistic EuroScore, % (IQR)	14.5 (8.6–24.2)	16.1 (9.6–25.2)	12.6 (8.0–23)	.030
High risk (>20%)	169 (30.6)	103 (36.1)	66 (25.1)	.012
Low risk (<10%)	154 (27.9)	71 (24.9)	83 (31.6)	.033
Left ventricular ejection fraction, % (SD)	53.8 (13.5)	53.9 (13.5)	53.7 (13.5)	.868
Mean transaortic gradient, mean (SD), mm Hg	45.3 (16.0)	45.2 (16.6)	45.3 (15.4)	.715
Aortic valve area, mean (SD), cm^2	0.73 (0.23)	0.72 (0.22)	0.74 (0.24)	.316
Periprocedural characteristics, n (%)				
Implantation site				
Catheterization laboratory	249 (45.1)	133 (46.7)	116 (44.1)	.548
Operating or hybrid room	303 (54.9)	152 (53.3)	147 (55.9)	
Approach				
Transfemoral	485 (87.9)	239 (83.9)	243 (92.4)	<.001
Transapical	43 (7.8)	35 (12.3)	7 (2.7)	
Transaortic	13 (2.4)	7 (2.5)	6 (2.3)	
Other	11 (2.0)	4 (1.4)	7 (2.7)	
Endotracheal intubation	239 (43.3)	154 (54.0)	82 (31.2)	<.001
Prosthesis type				
Balloon-expandable	292 (52.9)	149 (52.3)	139 (52.9)	.798
Self-expandable	246 (44.6)	130 (45.6)	116 (44.1)	
Antibiotic prophylaxis				
B-Lactam alone	438 (79.4)	220 (77.2)	217 (82.5)	.012
Vancomycin (alone or in combination)	23 (4.2)	18 (6.3)	4 (1.5)	
In-hospital outcomes (TAVR)				
Acute renal failure, n (%)	72 (13.0)	40 (14.0)	32 (12.2)	.569
Stroke, n (%)	26 (4.7)	14 (4.9)	12 (4.6)	.883
Major vascular complication, n (%)	39 (7.1)	25 (8.8)	14 (5.3)	.130
Major bleeding, n (%)	55 (10.0)	33 (11.6)	22 (8.4)	.236
New pacemaker implantation, n (%)	96 (17.4)	56 (19.7)	40 (15.2)	.185
Length of hospital stay, median (IQR), days	8 (6–14)	9 (7–15)	7 (5–13)	<.001

Data are presented as n (%), median (IQR), or mean (SD). Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SD, standard deviation.
[a]Time of TAVR was missing in 4 patients.

CC (7 [IQR, 5–13] days) versus the HC (9 [IQR, 7–15] days) ($P < .001$).

Characteristics and Clinical Outcomes of the Infective Endocarditis Episode Post–Transcatheter Aortic Valve Replacement

The characteristics and outcomes of the IE episode post-TAVR for the entire population and according to the timing of the TAVR procedure (CC and HC) are shown in Table 2. Overall, the IE episode was diagnosed after a median of 6.5 months (IQR, 2.0–15.9 months) following TAVR. Fever was the most frequent symptom at admission in both groups, but the proportion of patients presenting without fever was higher in the CC (HC vs CC: 21.1% vs 31.2%; difference, −10.1%; 95% CI, −17.5%% to −2.8%; $P = 0.004$). Acute heart failure at admission was common (HC vs CC: 42.5% vs 37.3%), while neurological symptoms (HC vs CC: 17.5% vs 15.6%) and systemic embolism (HC vs CC: 14.0% vs 9.9%) were less frequent (no differences between groups, $P > .05$ for all). The presumed source of entry was only identified in 280 patients (HC vs CC: 48.8% vs 52.5%) and urological infection was the most frequent source of bacteremia in both cohorts. Vegetations were identified in nearly two-thirds of the patients with no differences between groups regarding valve-involved

Table 2. Main Clinical Characteristics, Management, and Outcomes of Infective Endocarditis After Transcatheter Aortic Valve Replacement (TAVR), Overall and According to the Time of TAVR (Historical vs Contemporary Cohort)

	Overall (N = 552)[a]	Historical Cohort (n = 285)	Contemporary Cohort (n = 263)	Unadjusted *P* Value
Incidence of IE (per 1000 patient-years) (95% CI)	5.92 (5.28–6.63)	6.52 (5.54–7.67)	5.45 (4.65–6.38)	.123
Incidence of early IE (per 1000 patients) (95% CI)	3.02 (2.41–3.63)	4.89 (3.44–6.36)	2.29 (1.66–2.92)	<.001
Initial symptoms, n (%)				
Fever	409 (74.1)	225 (78.9)	181 (68.8)	.004
New-onset heart failure	219 (39.7)	121 (42.5)	98 (37.3)	.207
Neurological	92 (16.7)	50 (17.5)	41 (15.6)	.524
Systemic embolism	66 (12.0)	40 (14.0)	26 (9.9)	.130
Cutaneous	26 (4.7)	11 (3.9)	15 (5.7)	.320
Healthcare-associated infection, n (%)	229 (41.5)	112 (39.3)	113 (43.0)	.383
Echocardiographic findings, n (or n/N) (%)				
Vegetation	325/515 (63.1)	167/266 (62.8)	154/245 (62.9)	.986
No TAVR platform involvement	216 (39.1)	111 (39.0)	104 (39.5)	.862
Periannular complication	94/393 (23.9)	43/186 (23.1)	50/204 (24.5)	.747
New aortic regurgitation	54/421 (12.8)	27/190 (14.2)	27/217 (11.9)	.483
New mitral regurgitation	69/408 (16.9)	35/182 (19.2)	32/222 (14.4)	.195
Valves involved, n (%)				
Isolated TAVR prosthesis	265 (48.0)	138 (48.4)	125 (47.5)	.983
Mitral (native or prosthetic valve)	77 (14.0)	38 (13.3)	38 (14.5)	
Cardiac device	21 (3.8)	10 (3.5)	11 (4.2)	
Right-sided IE	7 (1.3)	4 (1.4)	3 (1.1)	
Other	182 (33.0)	95 (33.3)	86 (32.7)	
Causative microorganisms, n/N (%)				
Staphylococcus aureus	125/521 (24.0)	64/263 (24.3)	59/254 (23.2)	.768
Methicillin sensitive	105/521 (20.2)	49/263 (18.6)	55/254 (21.3)	.077
Methicillin resistant	20/521 (3.8)	15/263 (5.7)	5/254 (2.0)	
Coagulase-negative staphylococci	95/521 (18.2)	47/263 (17.9)	48/254 (18.9)	.763
Methicillin sensitive	61/521 (11.7)	35/263 (13.3)	26/254 (10.2)	.036
Methicillin resistant	28/521 (5.4)	8/263 (3.0)	20/254 (7.9)	
Enterococci	131/521 (25.1)	66/263 (25.1)	65/254 (25.6)	.897
Streptococci				
Oral streptococci	74/521 (14.2)	30/263 (11.4)	43/254 (16.9)	.071
S. gallolyticus (S. bovis)	26/521 (5.0)	12/263 (4.6)	14/254 (5.5)	.622
Others	23/521 (4.4)	16/263 (6.1)	6/254 (2.4)	.036
Culture negative	31/521 (6.0)	16/263 (6.1)	15/254 (5.9)	.923
Presumed source of entry, n (%)				
Unknown	272 (49.3)	146 (51.2)	125 (47.5)	.467
Procedural TAVR related	10 (1.8)	5 (1.8)	5 (1.9)	
Urological	47 (8.5)	18 (6.3)	29 (11.0)	
Odontological	22 (4.0)	8 (2.8)	12 (4.6)	
Pacemaker implantation	12 (2.2)	7 (2.5)	5 (1.9)	
Skin infection	20 (3.6)	12 (4.2)	8 (3.0)	
Vascular access	15 (2.7)	9 (3.2)	5 (1.9)	
Other	154 (27.9)	80 (28.1)	74 (28.1)	
Complications during infective endocarditis hospitalization, n/N (%)				
Any complication	354/517 (68.5)	185/266 (69.6)	168 (67.7)	.659
Heart failure	216/515 (41.9)	115/266 (43.2)	100/246 (40.7)	.554
Acute renal failure	191/476 (40.1)	112/251 (44.6)	78/222 (35.1)	.036
Septic shock	135/513 (26.3)	75/264 (28.4)	59/246 (24.0)	.257
Stroke	51/512 (10.0)	32/264 (12.1)	19/245 (7.8)	.101
Other systemic embolization	53/513 (10.3)	26/265 (9.8)	27/245 (11.0)	.655
Persistent bacteremia	125/450 (27.8)	57/214 (26.6)	68/233 (29.2)	.549
Surgery during IE hospitalization n/N (%)	100/532 (18.8)	48/277 (17.3)	52/251 (20.7)	.321
Time to surgery, median (IQR), days	16.5 (6.5–35)	17 (5–36)	14 (8–35)	.845
TAVR explantation, n/N (%)	64/96 (66.7)	30/47 (63.8)	34/49 (69.4)	.160
Leads removed, n/N (%)	18/96 (18.8)	7/47 (14.9)	11/49 (22.5)	
Other, n/N (%)	14/96 (14.6)	10/47 (21.3)	4/49 (8.2)	

Table 2. Continued

	Overall (N = 552)[a]	Historical Cohort (n = 285)	Contemporary Cohort (n = 263)	Unadjusted *P* Value
Follow-up outcomes				
Follow-up, median (IQR), months	14.4 (4.7–32.2)	20.6 (5.8–44.5)	11.6 (3.7–25.9)	
Total person-years	674			
In-hospital mortality,[b] n (%)	170 (32.0)	102 (36.4)	66 (26.6)	.016
1-year mortality rate, % (95% CI)	46.6 (42.3 to 51.3)	53.5 (47.6 to 59.6)	37.8 (31.5 to 44.9)	<.001[c]
Recurrence of IE, n/N (%)	46/382 (12.0)			
Surgery during follow-up, n/N (%)	11/382 (2.9)			

Values are n (%), or median (IQR), unless otherwise indicated. Abbreviations: CI, confidence interval; IE, infective endocarditis; IQR, interquartile range.

[a]Time of TAVR was missing in 4 patients.

[b]Data available in 532 patients.

[c]Log-rank.

distribution. Enterococci were the most common microorganisms in both cohorts, followed closely by *Staphylococcus aureus*. The episodes caused by methicillin-resistant coagulase-negative staphylococci were higher in the CC (HC vs CC: 3.0% vs 7.9%; difference, −4.9; 95% CI, −8.7% to −0.9%; *P* = .036). Among patients with early IE, a tendency toward an increased incidence of enterococci (HC vs CC: 25.5 vs 38.7; *P* = .136) along with a decreased proportion of *S. aureus* (HC vs CC: 35.3% vs 29.0%; *P* = .477) was observed.

The proportion of patients presenting with complicated IE (including heart or renal failure, systemic embolisms, or uncontrolled infection) for the entire population was 68.5% (95% CI, 64.5–72.5%). The complication rate was similar in both groups except for a lower rate of acute renal failure in the CC (HC vs CC: 44.6% vs 35.1%; difference, 9.5%; 95% CI, .7–18.3%; *P* = .036). The vast majority of patients were treated with antibiotics alone with no differences between groups in surgical intervention rates (HC vs CC: 17.3% vs 20.7%; *P* = .321) despite the high percentage of patients with surgery indication in both groups (HC: 82.1%; CC: 79.5%). There was no substantial temporal variation concerning the distribution of antibiotic regimens: β-lactam antibiotics alone (HC vs CC: 20.5% vs 24.4%), β-lactam in combination with aminoglycosides (HC vs CC: 30% vs 31.7%), or vancomycin alone or in combination with other antibiotics (HC vs CC: 32.9% vs 28.3%). Among those patients undergoing surgery, TAVR explantation was the most frequent intervention (HC vs CC: 63.8% vs 69.4%; *P* = .160). In-hospital death occurred in 170 patients, leading to an in-hospital mortality rate of 32.0% (95% CI, 28.0–35.9%) with a median survival of 22 days (IQR, 8–50 days). In-hospital mortality was lower in the CC (HC vs CC: 36.4% vs 26.6%; difference, 9.8%; 95% CI, 1.9–17.7%; *P* = .016). Patients who survived the index

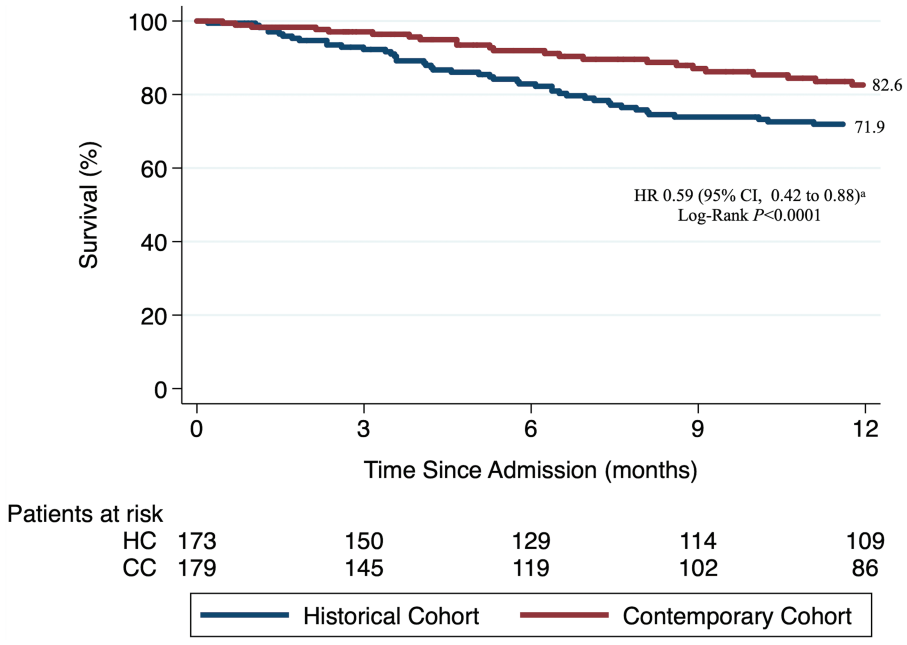

Figure 2. Kaplan–Meier estimate survival curve at the 1-year follow-up of patients who survived the infective endocarditis episode, comparing the HC and CC. [a]HC as reference. Abbreviations: CC, contemporary cohort; CI, confidence interval; HC, historical cohort; HR, hazard ratio.

Table 3. Factors associated with In-Hospital Mortality in Patients With Infective Endocarditis After Transcatheter Aortic Valve Replacement

	Univariate Analysis Hazard Ratio (95% CI)	Unadjusted *P* Value	Multivariate Analysis Hazard Ratio (95% CI)	Adjusted *P* Value
Baseline and TAVR features				
Logistic EuroScore[a]	1.02 (1.00–1.03)	.0099	1.02 (1.01–1.03)	.001
Chronic renal failure (at baseline)	1.71 (1.26–2.33)	.0007	…	…
Implantation site				
Catheterization laboratory	1 (Reference)		…	…
Operating or hybrid room	1.57 (1.14–2.16)	.0049	…	…
Approach				
Other	1 (Reference)		…	…
Transfemoral	.56 (.35–.90)	.0257	…	…
Post-TAVR acute renal failure	1.72 (1.17–2.55)	.0102	…	…
Presenting symptoms				
Neurological	1.82 (1.27–2.60)	.0020	…	…
New-onset heart failure	2.12 (1.55–2.91)	<.0001	1.40 (.95–2.06)	.086
Microorganism				
Staphylococcus aureus	2.24 (1.62–3.10)	<.0001	1.71 (1.16–2.52)	.006
Oral streptococci	.47 (.26–.84)	.0047	…	…
S. gallolyticus (S. bovis)	.92 (.86–.99)	.0023	…	…
In-hospital complications				
Heart failure	3.29 (2.36–4.59)	<.001	2.07 (1.36–3.15)	.001
Acute renal failure	3.30 (2.35–4.63)	<.001	2.54 (1.69–3.80)	<.001
Stroke	2.14 (1.41–3.25)	.0010	1.77 (1.11–2.80)	.016

Abbreviations: CI, confidence interval; TAVR, transcatheter aortic valve replacement.

[a]Per 1% increase.

hospitalization in the CC presented lower 1-year mortality rates (17.4%; 95% CI, 11.8–25.2%) compared with those who survived in the HC (28.1%; 95% CI, 21.8–35.8%; log-rank $P < .001$) (Figure 2).

Factors Associated With Clinical Outcomes

The uni- and multivariable-adjusted Cox model determining the independent factors associated with in-hospital mortality are shown in Table 3. A higher risk profile for TAVR as determined by the logistic EuroScore (adjusted hazard ratio [HRadj], 1.02; 95% CI, 1.01–1.03; $P = .001$), *S. aureus* etiology (HRadj, 1.71; 95% CI, 1.16–2.52; $P = .006$) and IE-related complications such as stroke (HRadj, 1.77; 95% CI, 1.11–2.80; $P = .016$), new-onset heart failure (HRadj, 2.07; 95% CI, 1.36–3.15; $P = .001$), and acute renal failure during index hospitalization (HRadj, 2.54; 95% CI, 1.69–3.80; $P < .001$) were independently associated with in-hospital mortality during the index IE episode.

DISCUSSION

This study, representing the largest cohort of definite IE post-TAVR to date, provides a comprehensive description along with a perspective on the temporal evolution of this life-threatening infection. The main study findings can be summarized as follows: (1) overall incidence rates of IE following TAVR remained similar, but the incidence of early IE was more than halved in the CC; (2) enterococci remained the most commonly identified microorganism, followed by *S. aureus*; (3) overall complications during the IE episode were frequent (~70%), irrespective of the TAVR/IE time period; (4) there were no differences between cohorts in IE management, with 8 out of 10 patients being treated conservatively despite the high proportion (>80%) of patients with a surgical indication; and (5) in-hospital and 1-year mortality rates were very high but progressively decreased over time.

Although the number of TAVR procedures has increased exponentially in the last years, the incidence of IE has remained comparable over time. Nevertheless, our findings reveal a significant downward trend in the rate of early IE (within 60 days post-TAVR). Early IE is essentially related to the TAVR procedure, in-hospital period, and very early follow-up. The combination of 2 important factors may partially explain the decline in early IE incidence: first, the evolution of the TAVR procedure over the last years with simplified (and less invasive) procedures and device iterations that have translated into earlier patient ambulation and shorter hospital stay; and second, the profile of TAVR recipients has evolved towards patients with a lower comorbidity burden, who are generally exposed to fewer invasive diagnostic and therapeutic procedures, and therefore have a potentially lower risk of IE. Our data show that patients in the HC presented more comorbidities leading to a higher surgical risk and longer hospitalization length. In contrast, despite being slightly older, low-to-moderate-risk patients were more represented in the CC.

Infective endocarditis post-TAVR was associated with a very high rate (~70%) of overall IE-related complications during the index hospitalization. Although heart failure, stroke, and persistent bacteremia rates were similar in both cohorts, there

was a substantial decline in acute renal failure incidence over time. This aspect may be partially explained by the lower rate of pre-existing renal impairment in the CC group. Also, aminoglycosides (associated with nephrotoxicity) were no longer recommended as first-line therapy for enterococci and methicillin-susceptible *S. aureus* in the latest American Heart Association and European Society of Cardiology guidelines [15, 16], and this may have also contributed to lowering the risk of acute renal failure. Of note, new-onset heart failure, acute renal failure, and stroke were independent predictors of in-hospital mortality. This highlights the importance of early identification of patients at high risk for complications who might benefit from aggressive therapies to improve clinical outcomes.

Previous studies on definite PVE have reported in-hospital mortality rates of approximately 20% [12]. The current study showed an even worse prognosis in TAVR recipients, with up to one-third of patients dying during the IE index hospitalization. The causes of such a high in-hospital mortality are probably multifactorial: first, the clinical profile of TAVR recipients, commonly elderly patients with a high comorbidity burden; second, IE diagnosis may be particularly challenging, with patients frequently presenting with atypical symptoms leading to a delay in treatment initiation; and third, the sensitivity of conventional imaging techniques for detecting vegetations seems relatively low compared with that reported in prior studies [17]. Nevertheless, there was a decreasing rate over time regarding in-hospital mortality, with a 9.8% absolute reduction in the most recent (vs HC) cohort. Although patients in the CC were older than those in the HC, they presented a much lower surgical risk profile, which likely reflects a better clinical status. Also, the growing use of novel imaging techniques (especially nuclear imaging) in recent years may have contributed to a more accurate diagnosis, leading to early treatment and improved outcomes in the CC. Unfortunately, data regarding time from initial symptoms to definite diagnosis were not available in most patients. Despite these improvements, the prognosis of patients who survived the initial IE episode remained uncertain, with a high mortality rate (close to 50%) at 1-year follow-up.

The most appropriate management of IE in patients post-TAVR remains unclear. Conservative treatment with only antibiotic therapy, even in the presence of severe IE-related complications, was the most frequent strategy (>80%), with no significant temporal trend changes. These results were in accordance with previous studies, which also reported very low rates of surgery and valve explantation (<15%) [18, 19]. Globally, surgery is the mainstay for the management of patients with complicated IE. Valve or cardiac device explantation is the treatment of choice, with some series reporting up to 40–50% of surgical interventions during IE index hospitalization [20–22]. Nevertheless, the evidence in TAVR patients is limited and surgical recommendations cannot always be extrapolated to this population, who frequently exhibit an increased comorbidity burden and high-risk profile. One study, including a high-risk cohort of patients developing IE post-TAVR, showed no benefit in terms of mortality between surgery and conservative management [23]. Our study shows that, despite the presence of surgery criteria in more than 8 out of 10 patients, only those with lower risk underwent surgery, irrespective of underlying IE-related complications. Further studies are needed to determine the optimal indications and timing of surgery in this challenging population.

Study Limitations

This is an observational, retrospective study, with the limitations and potential bias of data collection inherent in this design. Also, there was no external monitoring committee to verify the accuracy of data reported by each center. Finally, since the study included only individual data on patients with definite IE, the determination of risk factors for developing IE was not feasible. Although a large subsample including all TAVR patients (with and without IE post-TAVR) with individual follow-up data was used to evaluate the incidence of IE, the lack of follow-up information in the overall TAVR population from all participating centers is a limitation that could lead to potential bias.

Conclusions

Infective endocarditis after TAVR can be considered as a distinct entity among patients with PVE, with a singular microbiological profile, high incidence of IE-related complications, an unresolved role of surgery, and a poor prognosis. Data from the historical and contemporary cohorts showed similar IE incidence rates but temporal improvements regarding the incidence of early IE and clinical outcomes, with lower in-hospital and 1-year mortality rates in recent times. Further studies are needed to further improve the prevention and management of IE post-TAVR.

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