Infective Endocarditis After Transcatheter Aortic Valve Implantation

Results From a Large Multicenter Registry

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Background—We aimed to determine the incidence, predictors, clinical characteristics, management, and outcomes of infective endocarditis (IE) after transcatheter aortic valve implantation (TAVI).

Methods and Results—This multicenter registry included 53 patients (mean age, 79±8 years; men, 57%) who suffered IE after TAVI of 7944 patients after a mean follow-up of 1.1±1.2 years (incidence, 0.67%, 0.50% within the first year after TAVI). Mean time from TAVI was 6 months (interquartile range, 1–14 months). Orotracheal intubation (hazard ratio, 3.87; 95% confidence interval, 1.55–9.64; *P*=0.004) and the self-expandable CoreValve system (hazard ratio, 3.12; 95% confidence interval, 1.37–7.14; *P*=0.007) were associated with IE (multivariate analysis including 3067 patients with individual data). The most frequent causal microorganisms were *coagulase-negative staphylococci* (24%), followed by *Staphylococcus aureus* (21%) and *enterococci* (21%). Vegetations were present in 77% of patients (transcatheter valve leaflets, 39%; stent frame, 17%; mitral valve, 21%). At least 1 complication of IE occurred in 87% of patients (heart failure in 68%). However, only 11% of patients underwent valve intervention (valve explantation and valve-in-valve procedure in 4 and 2 patients, respectively). The mortality rate in hospital was 47.2% and increased to 66% at the 1-year follow-up. IE complications such as heart failure (*P*=0.037) and septic shock (*P*=0.002) were associated with increased in-hospital mortality.

Conclusions—The incidence of IE at 1 year after TAVI was 0.50%, and the risk increased with the use of orotracheal intubation and a self-expandable valve system. *Staphylococci* and *enterococci* were the most common agents. Although most patients presented at least 1 complication of IE, valve intervention was performed in a minority of patients, and nearly half of the patients died during the hospitalization period. **(*Circulation*. 2015;131:1566-1574. DOI: 10.1161/CIRCULATIONAHA.114.014089.)**

Key Words: endocarditis ■ heart valves ■ transcatheter aortic valve implantation

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Infective endocarditis (IE) is a rare but serious complication after surgical valve replacement, with an incidence of early IE (within the first year) between 0.1% and 2.3% regardless of the type of prosthetic valve (biological or mechanical).[1,2] The clinical features, causes, complications, and outcomes associated with this syndrome have been well documented in patients undergoing surgical valve replacement and have facilitated the implementation of the most appropriate management therapies, although mortality remains very high.[3,4]

Clinical Perspective on p 1574

Transcatheter aortic valve implantation (TAVI) represents a paradigm shift in the treatment of aortic stenosis in patients considered at high or prohibitive surgical risk.[5] The reported rates of early IE after TAVI have varied from 0.1% to 3.03%,[6–8] with no differences compared with surgical aortic valve replacement, as shown in the prospective randomized Placement of Aortic Transcatheter Valves (PARTNER) trial.[6] However, data on the clinical characteristics, causes, treatment, and clinical outcomes of IE after TAVI are scarce and limited to case reports and small series, which indeed may suffer from publication bias.[9] Such information is crucial to improve both the diagnosis and management of this entity in the context of TAVI. The particular features of TAVI candidates and the specific design of transcatheter valve prostheses, including a much higher amount of metal (stent frame) around the valve leaflets compared with surgical valves, may indeed alter the outcome and management of IE. The objectives of this multicenter registry were thus to evaluate the incidence, predictors, and clinical characteristics of IE after TAVI and to determine the current strategies of management and clinical outcomes in a large cohort of patients suffering from IE after TAVI.

Methods

This multicenter registry of IE after TAVI collected retrospectively all cases with this complication from 21 centers in North America, South America, and Europe from 2007 to 2014. The definition of IE was based on the modified Duke criteria[10] or the surgical findings. All cases meeting the definite criteria of IE were included. Taking into consideration the low sensitivity of the modified Duke criteria in the setting of prosthetic valve endocarditis,[1,2,4] any case considered possible IE was evaluated and finally either included or not in the study on the basis of the consensus of 3 investigators (I.A.S., J.L., and J.R.C.). The gathered data included the main baseline clinical, echocardiographic, and procedural characteristics and follow-up outcomes. IE features included the timing of initial symptoms and their description; echocardiographic, multiple blood culture, and microbiological findings; complications; management; and short-term and midterm outcomes. Early IE was defined as any IE occurring within 12 months after the TAVI procedure.[1,2] IE related to healthcare procedures was defined in accordance with the criteria of Friedman et al.[11] The clinical events were defined according to the Valve Academic Research Consortium-2 criteria.[12]

In addition to the IE data, all centers were asked to provide data on the entire population who had undergone TAVI in each center and did not suffer from IE (total, 7891 patients). All centers had a dedicated TAVI database, and all of them followed up their patients through clinical visits or phone contact. The mean follow-up of the TAVI population at the time of data collection was 1.1±1.2 years, and follow-up completeness ranged from 97.2% to 100%, depending on the center. Data from the non-IE population included mean age and logistic EuroSCORE, percentage of men/women, and the main baseline characteristics (including classic risk factors for endocarditis). Data on valve type, approach, and other procedural details were also gathered. A total of 12 centers including 3067 patients also provided individual data on baseline, procedural, and follow-up features from their entire TAVI population. All studies were performed in accordance with the local ethics committee of each center, and all patients signed informed consent forms before the procedures.

Statistical Analysis

Categorical variables are reported as number (percent) and continuous variables as mean (SD) or median (25th to 75th interquartile range), depending on variable distribution. Group comparisons were analyzed with the Student *t* test or Wilcoxon rank-sum test for numeric variables and the χ^2 or Fisher exact test for categorical variables. A Cox proportional hazard analysis including 3067 patients from 12 centers with individual data information was performed to determine the independent predictors of IE. The variables with a value of $P<0.05$ in the univariate analysis were included in the model. Survival at the 1-year follow-up was presented as Kaplan–Meier curves. All hypothesis testing was 2 sided with a significance level of 0.05. Data were analyzed with the statistical package SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

A total of 53 cases of IE after TAVI were identified of 7944 patients who underwent TAVI (incidence, 0.67%; 0.50% at 1-year follow-up, 0.19% within the 2 months after the procedure). Fifty-one of these patients had a diagnosis of definite IE, and 2 patients with a diagnosis of possible IE were also included. Three additional cases with possible IE had been evaluated and subsequently excluded as a result of a lack of supportive echocardiographic, clinical, or microbiological findings. The main clinical and procedural characteristics of the IE patients compared with the rest of the study population are shown in Table 1. Patients with IE were younger (P=0.033) and had a higher risk profile as determined by logistic EuroSCORE (P=0.010) compared with the non-IE population. Most patients (76%) in both groups underwent the procedure by the transfemoral approach, and most procedures (60%) were performed in a catheterization laboratory, with no differences between IE and non-IE patients. The balloon-expandable Edwards valve (Edwards Lifesciences, Irvine, CA) was the most commonly used in both groups, but the percentage of use of the self-expandable CoreValve system (Medtronic, Minneapolis, MN) was higher (P=0.003) in the IE group. The use of general anesthesia with orotracheal intubation for the TAVI procedure was also more frequent (P=0.037) in the IE group. All participating centers used systematic antibiotic prophylaxis during the TAVI procedure. Cephalosporins (including cefazoline, cefuroxime, cephamandole, and ceftriaxone) were used in 14 of the 21 participating centers (67%) and were administered as a single dose in all but 2 centers, which repeated 2 to 3 doses of antibiotics after the procedure. Six centers (28%) used vancomycin routinely, and 1 center (5%) used piperacilline/tazobactam as antibiotic prophylaxis.

The main procedural and 30-day outcomes after TAVI are detailed in Table 1 and Table I in the online-only Data Supplement, respectively.

Univariate and multivariate analyses to identify the predictors of IE were performed in a cohort of 3067 patients from the 12 centers that provided individual data for their entire TAVI population, and the results of these analyses are shown in Table II in the online-only Data Supplement. A total of 29

Table 1. Main Baseline and Periprocedural Characteristics According to the Occurrence of IE

Variables	Global TAVI Population (n=7891)	TAVI-IE Population (n=53)	*P* Value
Baseline characteristics			
Age, y*	81±8	79±8	0.033
Female sex, n (%)	3797/7170 (53.0)	23 (43.4)	0.165
Diabetes mellitus, n (%)	1279/4086 (31.3)	19 (35.8)	0.474
COPD, n (%)	1079/4086 (26.4)	18 (34.0)	0.212
eGFR <60 mL/min, n (%)	1908/4086 (46.7)	22 (41.5)	0.448
LogEuroSCORE, %*	20.24±12.99	24.85±13.82	0.010
Periprocedural characteristics			
Implantation site, n (%)			
Catheterization laboratory	4450/7355 (60.5)	32 (60.4)	0.986
Operating/hybrid room	2905/7355 (39.5)	21 (39.6)	
Type of antibiotic prophylaxis, n (%)			
Penicillins	1748 (22.2)	9 (17.0)	0.108
Cephalosporins	4748 (61.8)	30 (56.6)	
Vancomycin	1265 (16.0)	14 (26.4)	
Type of valve, n (%)			
Self-expandable CoreValve	1562/7891 (19.8)	19 (35.8)	0.003
Balloon-expandable Edwards valve	6329/7891 (80.2)	34 (64.2)	
Approach, n (%)			
Transfemoral	5568/7355 (75.7)	40 (75.5)	0.970
Transapical	1773/7355 (24.1)	10 (18.9)	0.375
Transaortic	206/7355 (2.8)	2 (3.8)	0.999
Orotracheal intubation, n (%)	3528/5054 (69.8)	44 (83.0)	0.037
Device success, n (%)	7654/7891 (97.0)	50 (94.3)	0.469
Acute kidney injury, n (%)	1341/7355 (18.2)	11 (20.8)	0.721
PPM implantation, n (%)	588/4086 (14.4)	6 (11.3)	0.529
Mean residual gradient, mm Hg	11±3	12±5	0.299
Aortic valve area, cm^2	1.8±0.5	1.7±0.3	0.432
Left ventricular ejection fraction, %	58±14	56±12	0.199
Residual aortic regurgitation >2, n (%)	970/7355 (13.2)	8 (15.1)	0.683
Length of ICU stay, d	3.3±7.9	3.4±3.8	0.897
Length of hospital stay, d	9.8±10.8	10.3±7.6	0.721

Variables are expressed as mean (SD) when appropriate. COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICU, intensive care unit; IE, infective endocarditis; PPM, permanent pacemaker; and TAVI, transcatheter aortic valve implantation.

*Age information available for all patients. LogEuroSCORE and Society of Thoracic Surgeons score available for 4086 patients.

cases from these centers were diagnosed with IE after TAVI. Among the baseline and periprocedural variables, the sole 2 factors associated with a higher rate of IE in the univariate analysis were the use of a self-expandable CoreValve system (*P*=0.025) and orotracheal intubation (*P*=0.021); these 2 factors remained independent predictors of IE in the multivariate analysis (hazard ratio, 3.12; 95% confidence interval, 1.37–7.14; *P*=0.007 for self-expandable CoreValve use; hazard ratio, 3.87; 95% confidence interval, 1.55–9.64; *P*=0.004 for orotracheal intubation).

Characteristics of IE After TAVI

The median time between TAVI and the first symptoms of IE was 6 months (interquartile range, 1–14 months), with up to 40 patients (75.5%) developing the initial symptoms of IE within the year after TAVI, which represents an incidence of early IE of 0.50%. The development of IE symptoms during the hospitalization after TAVI occurred in 1 patient. The time distribution from TAVI to the first symptoms of IE is depicted in Figure I in the online-only Data Supplement.

The main clinical features of IE after TAVI are shown in Table 2. Fever (71.7%) and heart failure (58.5%) were the most common symptoms of IE. Exposure to a procedure at risk for bacteremia before IE was identified in 27 patients (51%), most commonly urologic, gastrointestinal, and odontological sources, and after healthcare procedures in 21 patients (39.6%), distributed as follows: intravenous therapy within the prior 30 days (15 patients), hospitalization in an acute care facility for ≥2 days within the 3 months before the infection (4 patients), and resident in a nursing home or long-term care facility (2 patients).

Table 2. Main Clinical Characteristics, Management, and Outcomes of IE After TAVI (n=53)

Variables	
Time from TAVI, mo	6 (1–14)
Initial symptoms, n (%)	
Fever	38 (71.7)
Heart failure	31 (58.5)
Neurological	4 (7.5)
Cutaneous	2 (3.8)
Hyporexia, weight loss	11 (20.8)
Exposure to sources of bacteremia before IE, n (%)	
Unknown	27 (50.9)
Odontological	3 (5.7)
Urologic	4 (7.5)
Skin infection	5 (9.4)
Pacemaker implantation	1 (1.9)
Health care related	21 (39.6)
Antibiotic prophylaxis, n (%)*	31 (58.5)
Microorganisms, n (%)	
Coagulase-negative Staphylococci	13 (24.5)
Staphylococcus aureus	11 (20.8)
Enterococci	11 (20.8)
Streptococcus viridans	3 (5.7)
Unknown (negative cultures)	2 (3.8)
Other	13 (24.5)
Echocardiographic findings, n (%)	
Vegetations	41 (77.4)
Aorto-atrial fistulas	2 (3.8)
Aortic pseudoaneurysm	2 (3.8)
Aortic abscess	8 (15.1)
New aortic regurgitation (transvalvular)	8 (15.1)
New mitral regurgitation	10 (18.9)
IE complications, n (%)	
Heart failure	36 (67.9)
Acute kidney injury	29 (54.7)
Septic shock	11 (20.8)
Stroke	4 (7.5)
Systemic embolism	5 (9.4)
Persistent infection	15 (28.3)
Management and outcomes, n (%)	
Valve intervention	6 (11.3)
Surgical valve explantation	4 (7.5)
Valve-in-valve procedure	2 (3.8)
In-hospital death	25 (47.2)
Death at follow-up	13 (24.5)
Cumulative death	38 (71.7)

Values are expressed as median (interquartile range) when appropriate. IE indicates infective endocarditis; and TAVI, transcatheter aortic valve implantation.

*Antibiotic prophylaxis before exposition to door of entry.

Most (81.8%) causal agents of IE after TAVI were considered "typical" microorganisms. Coagulase-negative *staphylococci* were the most frequent bacteria (24.5%), followed by *Staphylococcus aureus* (21%) and *enterococci* (21%). Three cases of IE (5.7%) were caused by oral (formerly *Viridans*) *streptococci*, all of them >1 year after valve implantation. Methicillin-resistant Gram-positive microorganisms were the cause of IE in 6 patients (11.3%), and in 13 patients (24.5%), IE was caused by other atypical agents, including *Serratia* (n=1)*, Acinetobacter iwofii* (n=1)*, Candida lusitaniae* (n=1)*, and Escherichia coli* (n=1). The type of microorganism according to the time from TAVI procedure to IE is shown in Figure II in the online-only Data Supplement. The main individual clinical and procedural characteristics, exposure to procedures at risk for bacteremia, and criteria for the diagnosis of IE ordered according to the type of microorganism are shown in Table III in the online-only Data Supplement.

Echocardiographic findings revealed the presence of vegetations in 41 patients (77.4%), located as follows: transcatheter valve leaflets (21 patients, 39.6%), stent frame (9 patients, 17.0%), and mitral valve (11 patients, 20.7%). Paravalvular extension of the infection was diagnosed in 12 patients (22.6%), and this included the presence of abscess, fistulas, and pseudoaneurysm in 8 patients (15.1%), 2 patients (3.8%), and 2 patients (3.8%), respectively. Vegetations anchored to the stent frame were more frequently found in patients treated with a self-expandable valve device (31.6% versus 8.8% in the balloon-expandable group; P=0.055), but no differences were found concerning paravalvular extension. The intracardiac location of the infection is depicted schematically in Figure 1. Moderate or severe aortic regurgitation at the time of admission for IE was detected in 14 patients (26.4%), newly described in 8 patients (15.1%). The mean transvalvular gradient was 17.2±10.3 mm Hg (increase of 4.9±5.1 mm Hg compared with hospital discharge after TAVI; P=0.003); the mean valve area was 1.6±0.4 cm^2 (compared with 1.7±0.3 cm^2 at hospital discharge after TAVI; P=0.199); and mean left ventricular ejection fraction was 57±12% (compared with 56.5±12.2% at hospital discharge after TAVI; P=0.140). Moderate or severe mitral regurgitation was present in 23 patients (43.4%), and an increase in the degree of mitral regurgitation compared with echocardiography after TAVI was observed in 10 patients (P=0.279). Perforation of the anterior mitral leaflet was found in 2 patients. Globally, 13 patients (24.5%) presented affection of the mitral valve, as summarized in Figure 1: native mitral valve alone in 7 patients (13.2%), prosthetic mitral valve alone in 4 patients (7.5%), and native mitral valve plus transcatheter aortic valve in 2 patients (3.8%).

Management and Clinical Outcomes of IE After TAVI

Prolonged antibiotic regimens (≥4 weeks or until death) were administered in all cases on IE diagnosis. β-Lactam antibiotics were used in 21 patients (39.6%), gentamycin in 20 patients (37.7%), and vancomycin in 16 patients (30.2%). Rifampicin was administered empirically in 7 patients with IE related to both *S aureus* and *S epidermidis*, and daptomycin was used in 5 of the 6 patients with IE related to methicillin-resistant germs.

Complications of IE were observed either at hospital admission or during the follow-up period in 46 patients (86.8%) and

are summarized in Table 2. A total of 46 patients (86.8%) had at least 1 indication for valve intervention according to current guidelines,[1,2] and this included heart failure in 31 patients (58.4%), septic shock in 11 patients (26.8%), methicillin-resistant *S aureus* in 3 patients (7.3%), structural complications in 16 patients (30.2%), large vegetations (>15 mm) in 6 patients (14.6%), and systemic emboli in 5 patients (12.2%). New intervention after IE was performed in only 6 patients (11.3%). The main individual data of the patients who had new intervention after IE are summarized in Table IV in the online-only Data Supplement. Two patients had IE located at the mitral valve leading to severe mitral regurgitation and underwent successful mitral valve replacement. Another 2 patients with new severe aortic regurgitation but without vegetations completed antibiotic treatment and, on verification of the healing of the infection, underwent a new TAVI procedure (valve-in-valve procedure with a self-expandable valve in both cases) to correct the sequelae (aortic regurgitation) of IE. Both patients had uneventful in-hospital and follow-up outcomes at 3 and 6 months, respectively. Finally, 2 patients who required aortic valve replacement as a result of mechanical complications of IE died during the postoperative period.

In-hospital death occurred in 25 patients (47.2%). The main baseline, procedural and IE characteristics of the patients who died compared to those who survived the initial in-hospital period are shown in Table 3, and the main individual characteristics of the patients who suffered in-hospital death are summarized in Table V in the online-only Data Supplement. The factors associated with in-hospital death were prior valve surgery (P=0.034) and the occurrence of IE complications such as heart failure (P=0.037) and septic shock (P=0.002).

The mean follow-up of the 28 patients who survived the in-hospital period was 13±15 months. A total of 13 additional patients died during the follow-up period (10 of them within the first year after hospital discharge) as a result of renal failure (3 patients, including 2 recurrences of IE), heart failure (3 patients), sudden death (2 patients), multiorgan failure caused by IE recurrence (2 patients), gastric bleeding (1 patient), pneumonia (1 patient), and lung cancer (1 patient). The Kaplan–Meier survival curves at the 12-month follow-up for the population with IE after TAVI are shown in Figure 2. Relapsed IE within the first year of the index IE episode was diagnosed in 4 patients (14.3% of the patients who survived the initial IE episode), none of whom had undergone intervention at an IE index hospitalization.

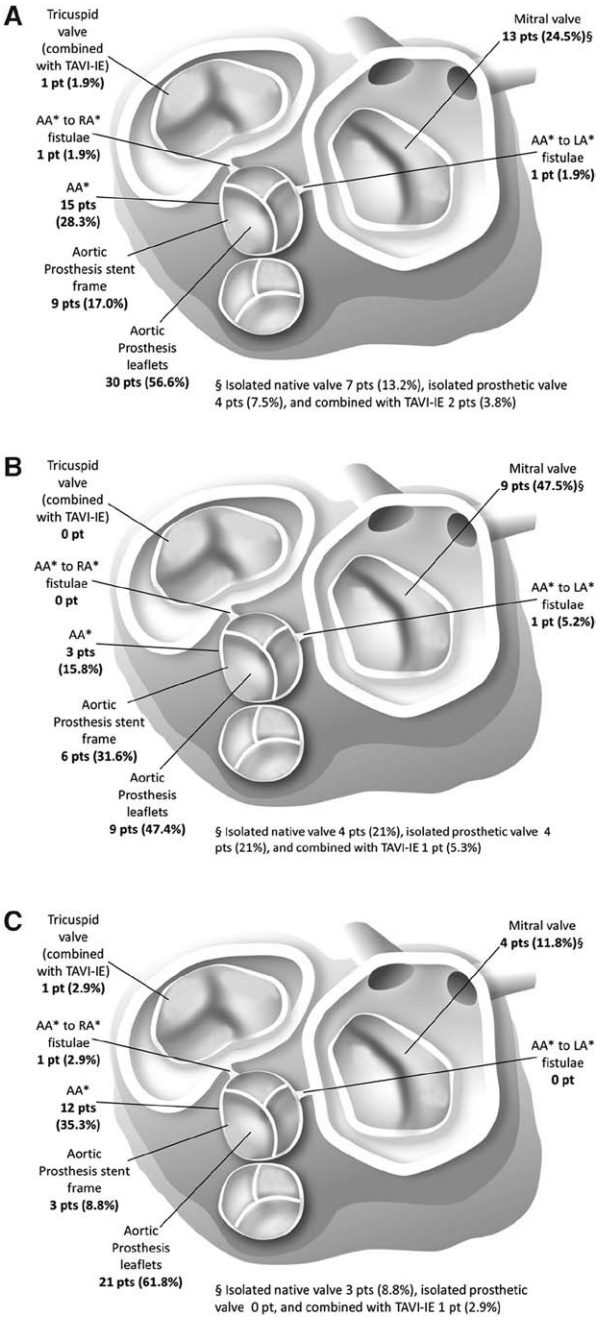

Figure 1. Schematic representation of the location of infective endocarditis (IE) in patients with previous transcatheter aortic valves. **A**, Global, n=53. **B**, Self-expandable CoreValve, n=19. **C**, Balloon-expandable Edwards valve, n=34. AA indicates ascending aorta; LA, left atrium; RA, right atrium; and TAVI, transcatheter aortic valve implantation.

Discussion

The proportion of patients with surgical prosthetic valve IE has increased progressively in the last few years and currently accounts for 10% to 30% of all patients diagnosed with IE.[1–3] The prevalence of IE in patients with a previous prosthetic valve has ranged from 1% to 6%, with an incidence of 0.3% to 1.2% within the first year after the intervention,[1,2,13–15] similar to the incidence of 0.5% observed in the present study. This rate is also consistent with previous smaller TAVI studies (0.1%–3.03%).[6–8] One would expect that a less invasive procedure such as TAVI would be associated with a lower rate of infective complications such as IE.[16–18] On the other hand, the very high exposure to healthcare procedures, older age, and higher amount of metal prosthesis in patients undergoing TAVI may contribute to increase the risk of IE in this specific population. In addition, possible leaflet damage during the process of crimping and deployment of the transcatheter valve may contribute to increasing the likelihood of IE.[19]

Orotracheal intubation and the use of a self-expandable valve system were associated with IE after TAVI. It has been shown that orotracheal intubation is associated with bacteremia in up to 12% of patients,[20] and this risk further increases in cases of difficult intubation,[20] which may be more frequent

in the TAVI population as a result of older age and degenerative changes (eg, kyphosis). In addition, a potential increased burden of instrumentation (eg, venous lines) in these patients may have played a role. The bacteriology of IE patients with a history of intubation did not point specifically to oral organisms. Furthermore, the time interval between intubation and infection did not suggest a causal link of the intubation procedure and the causal bacteremia. Intubation may therefore be a marker of patients with more severe illness who have increased susceptibility to bacteremia from a spectrum of infections or procedures. Future studies are needed to further explore this association and its pathophysiological mechanisms. Future studies should also determine whether the increasing use of local (versus general) anesthesia during TAVI procedures translates into a reduction in IE. The implantation of a self-expandable valve was associated with a risk of IE as much as twice as high as that of a balloon-expandable valve system. There is no clear explanation for this finding, and previous data on IE after self-expandable valve implantation are scarce, precluding any illuminating comparison with our data.[21] Differences between the 2 transcatheter systems in terms of the design, preimplantation processing of valve tissues, and delivery system and procedure may, at least in part, contribute to explain this higher rate of IE observed with the self-expandable CoreValve system. In particular, the much larger stent frame of self-expandable devices and the larger contact surface between the frame and the native tissues can act as potential anchoring and disseminating points during bacteremia. The fact that most patients with vegetations at the level of the stent frame had received a self-expandable valve would support this mechanistic hypothesis. In addition, many other factors such as the distribution of shear gradients and the amount of turbulence, the degree of endothelialization, paravalvular regurgitation, and other undescribed confounders could have contributed. However, only large randomized trials with considerable follow-up comparing these 2 types of devices will be able to definitely determine whether IE is partially determined by a valve type effect.

IE After TAVI: Microbiological Findings

As with IE in the general population, the main causative microorganisms of IE after TAVI were, in order of frequency, *staphylococci*, *streptococci*, and *enterococci*.[1,2] In the last few decades, *staphylococci* have become the leading cause of IE, and *S aureus* is currently the main cause of prosthetic valve endocarditis.[14,15,22–24] On the other hand, an increased presence of *enterococci* has been reported in previous series of IE,[22] and this was the most frequent agent in our study in those cases diagnosed within the first 2 months after TAVI. Importantly, this agent is a common groin contaminant.

A potential door of entry of IE was identified in ≈50% of patients, which is consistent with previous studies on IE.[3] However, the timing between procedures and onset of infection was often prolonged beyond the range of likely causality. Of note, close to one fifth of the cases occurred after urologic or gastrointestinal examinations, both of which are very frequent in the current TAVI population. In addition, a high rate of healthcare procedures was found within the months before the diagnosis of IE. These data suggest the need for additional studies to evaluate the potential usefulness of anti-infective preventive measures in this high-risk group of patients.

Table 3. Baseline Characteristics and IE Features According to the Occurrence of In-Hospital Death

Variables	Absence of In-Hospital Death (n=28)	In-Hospital Death (n=25)	*P* Value
Baseline characteristics			
Age, y	79±8	78±8	0.683
Male sex, n (%)	12 (42.9)	11 (44.0)	0.933
Diabetes mellitus, n (%)	10 (35.7)	9 (36.0)	0.933
COPD, n (%)	8 (28.6)	10 (40.0)	0.380
eGFR <60 mL/min, n (%)	14 (50.0)	8 (32.0)	0.184
LogEuroSCORE, %	28.3±15.0	20.8±12.3	0.354
Previous valve surgery, %	2 (7.1)	8 (32.0)	0.034
Mean aortic gradient, mm Hg	49.7±12.6	46.7±13.5	0.445
LVEF, %	57.7±12.0	53.6±13.3	0.254
IE features			
Time from TAVI, d	235±315	324±314	0.319
Microbiological profile, n (%)			
Staphylococcus aureus	6 (21.4)	5 (20)	0.898
MRSA	2 (7.1)	1 (4.0)	0.999
Coagulase-negative Staphylococci	7 (25.0)	6 (24.0)	0.933
Enterococci	8 (28.6)	3 (12)	0.183
Viridans streptococci	2 (7.1)	1 (4.0)	0.999
Polymicrobial	1 (3.6)	1 (4.0)	0.999
Negative cultures	0 (0)	2 (8.0)	0.218
Complications, n (%)			
Periannular complications	11 (39.3)	13 (52)	0.319
Heart failure	11 (39.3)	17 (68.0)	0.037
Acute kidney injury	13 (46.4)	16 (64.0)	0.200
Septic shock	1 (3.6)	10 (40)	0.002
Stroke	0 (0)	3 (12.0)	0.098
Systemic embolism	2 (7.1)	3 (12.0)	0.658
Persistent infection	5 (17.9)	10 (40.0)	0.074
Surgical treatment, n (%)	4 (14.3)	2 (8.0)	0.672

Values are expressed as mean (SD) when appropriate. COPD indicates chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration; IE, infective endocarditis; LVEF, left ventricular ejection fraction; MRSA, methicillin-resistant *Staphylococcus aureus*; and TAVI, transcatheter aortic valve implantation.

IE After TAVI: Clinical and Imaging Features

The symptoms of IE in TAVI patients are clearly determined by their comorbidities and biological status. Among other features, the presence of fever was less frequent (75%) than in cases of IE in the general population (90%),[1–3] probably as a result of the relatively anergic condition of patients undergoing TAVI nowadays. In addition, nonspecific symptoms such as asthenia or weight loss were the only symptoms in up to one fifth of the patients. It is therefore very important to maintain a low threshold for investigation of IE in such patients to avoid underdiagnosis. In addition, the occurrence of a new

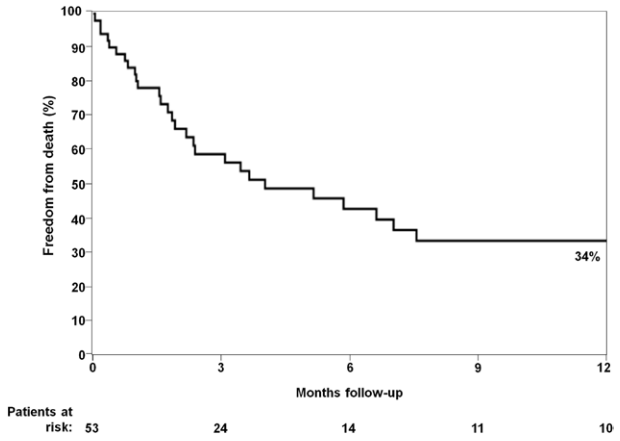

Figure 2. Kaplan–Meier survival curves at the 12-month follow-up in patients diagnosed with infective endocarditis (IE) after transcatheter aortic valve implantation (time 0 represents the time of IE diagnosis).

regurgitant heart murmur, an important sign for the diagnosis of IE, may be less valuable in TAVI patients because of their high rate of residual paravalvular leaks and mitral insufficiency after the procedure.[5] Finally, the development of heart failure (>50%) was very common, and this may reflect the poorer cardiovascular status of TAVI candidates, with a higher prevalence of reduced left ventricular ejection fraction and myocardial fibrosis, in addition to the higher rates of residual aortic regurgitation compared with patients who receive surgical valve prostheses.[3] On the other hand, the rate of embolic stroke (7.5%) as the first manifestation of IE was less common than in previous series (20%–40%).[1,2,25]

The presence of vegetations was detected in 77.4% of patients with IE after TAVI. This relatively high rate may have been attributable to a diagnostic bias (doubtful cases were not included) but may also be related to the extensive stent frame of transcatheter valves (involved in 17% of patients) or to disease of other valves (involved in 26%), particularly resulting from significant untreated mitral disease.[26] It is interesting to note that, in addition to the occurrence of new or an increase in aortic regurgitation in 15.1% of patients (transvalvular in all but 2 cases), a mean increase in valve gradient was observed at hospital admission in patients diagnosed with IE after TAVI. This may reflect either an early degeneration or subclinical valve thrombosis as a predisposing factor for IE but can also be related to hemodynamic changes during the infection; more pathological data are needed to confirm these findings.

Management and Outcomes of IE in TAVI Patients

According to the Euro Heart Survey,[14] the current rate of cardiac surgery during hospitalization in patients suffering from prosthetic valve IE is ≈50%. However, in our study, the rate of reintervention was as low as 11%, one of the lowest rates of reintervention in prosthetic valve IE ever reported. Importantly, at least 1 complication requiring reintervention according to the guidelines occurred in most patients (≈90%), and this underscores even more the high degree of undertreatment in this population. The very high surgical risk of this specific population, in addition to the technical challenge of removing a large stent frame adherent to the ascending aorta (particularly for self-expandable valves), may explain the low rate of reintervention. Finally, a valve-in-valve procedure was selected in 2 patients for treating the sequelae of IE (severe aortic regurgitation) after completion of the antibiotic treatment and verification of the absence of persistent infection. Although this is not the optimal treatment in a patient with prior IE, it probably remains a reasonable alternative for patients with heart failure and no surgical option. Future studies will have to determine the rate of IE recurrences with such a treatment, but it must be considered that, in complicated cases or those affected by aggressive agents such as *S aureus*, which are very difficult to eradicate despite adequate antibiotherapy (4 of 5 patients with methicillin-resistant microorganisms treated with daptomycin died), surgery remains the only effective therapy.[27–29]

IE is a life-threatening condition, with a risk of in-hospital mortality of 15% (10%–22%), which increases up to 40% (23%–40%) in cases of prosthetic valve IE.[3,24,30–32] The cumulative mortality rate at the 1-year follow-up is ≈30% overall and 45% for prosthetic valve IE.[3,14,15,24,33–35] The in-hospital (close to 50%) and 1-year (66%) mortality rates associated with IE after TAVI are therefore among the highest ever reported in the IE field. Importantly, the extremely poor results obtained with a more conservative strategy, even in the presence of complications such as heart failure and septic shock, highlight the importance of considering reintervention in such patients despite the very high surgical risk.

Limitations

The reporting of cases of IE was done on a voluntary basis, and there was no external monitoring or event adjudication committee to verify the accuracy of the data reported by each center. The results concerning predictive factors of IE have to be interpreted with caution. Although mean baseline and procedural data from non-IE patients were obtained from all centers, individual data for a comprehensive multivariate analysis were obtained for fewer than half of the patients, and this may have influenced the results concerning the independent predictors of IE. In addition, the influence of confounding factors other than those included in the multivariate model cannot be ruled out.

Conclusions

The rate of IE after TAVI was <1%/y, similar to that of prosthetic valve endocarditis following surgical aortic valve replacement. The use of orotracheal intubation was associated with an increased rate of IE, mainly by *S aureus*. However, neither bacteriology nor timing suggested a direct link between intubation and infection. The role of staphylococcal colonization (with broad exposure rates throughout health care facilities) and the risk of TAVI-associated IE needs further exploration, especially given the potential impact for antibiotic prophylaxis protocols. The finding of a higher rate of IE among patients who had received a self-expandable CoreValve is also intriguing and requires further confirmation. The microbiological profile of IE after TAVI highlights the important role of health care–related infections in such patients (in addition to *enterococci*), with *S aureus* and *coagulase-negative staphylococci* accounting for nearly half of the cases. This outlines the importance of reinforcing

an aseptic technique during healthcare procedures in such a high-risk group of patients. The location of the infection, with a significant proportion of cases exhibiting vegetations outside the prosthetic valve leaflets (at either the level of the stent frame or the mitral valve) reflects the particularities of this population/procedure, with a significant amount of metal in the ascending aorta and a high proportion of patients with mitral disease left untreated at the time of the procedure. The vast majority of patients had complications of IE, but only a minority received surgical treatment, also differing from previous prosthetic valve IE series and probably reflecting the very high surgical risk of the TAVI population. However, the prognosis of patients with IE after TAVI was ominous; close to half of the patients died in hospital, and only one third were still alive at 1 year after the index IE. Importantly, mortality was determined mainly by IE complications, suggesting the need for a more aggressive approach (as recommended by the guidelines) in these patients to improve clinical outcomes. While we await for future studies to determine whether a more invasive approach translates into improved outcomes in the context of IE after TAVI, a careful case-by-case evaluation by the heart team remains of major importance in such a challenging and high-risk group of patients.

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CLINICAL PERSPECTIVE

Data on the predictors, causes, clinical characteristics, treatment, and clinical outcomes of infective endocarditis (IE) after transcatheter aortic valve implantation are scarce. The present multicenter international registry reports 53 cases of IE among 7944 patients who underwent transcatheter aortic valve implantation, representing a 1 year incidence of 0.5% (similar to that reported for surgical prosthetic valves). The 2 factors associated with IE were orotracheal intubation and use of the self-expandable CoreValve system. However, no clear mechanisms linking these factors to IE were found, and further research is needed to confirm these findings. The microbiological profile of IE after transcatheter aortic valve implantation highlighted the important role of healthcare–related infections in such patients (in addition to *enterococci*), with Staphylococcus *aureus* and *coagulase-negative staphylococci* accounting for nearly half of the cases. This finding highlights the importance of reinforcing meticulous aseptic techniques during healthcare procedures. The location of the infection, with more than one third of patients exhibiting vegetations outside the prosthetic valve leaflets (at either the level of the stent frame or the mitral valve), reflects the particularities of this population/procedure, with a significant amount of metal in the ascending aorta and a high proportion of patients with mitral disease left untreated. Although close to 90% of patients developed complications, only 11% of them received surgical treatment, probably reflecting the very high surgical risk profile of this population. However, the prognosis was ominous; close to half of the patients died in hospital, and only one third were still alive at 1 year after the index IE. These results provide important insight into IE after transcatheter aortic valve implantation and should contribute to improving the management of this life-threatening entity.

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