Perivalvular Extension of Infective Endocarditis after Transcatheter Aortic Valve Replacement

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Summary:

Perivalvular extension was diagnosed in 18.1% of patients with infective endocarditis after transcatheter aortic valve replacement. Chronic kidney disease and coagulase negative streptococci were risks factors of this serious complication. Surgery was associated with better outcomes.

ABSTRACT

***Background**:* Infective endocarditis (IE) following transcatheter aortic valve replacement (TAVR) has been associated with a dismal prognosis. However, scarce data exist on IE perivalvular extension (PEE) in such patients.

Methods: This multicenter study included a total of 579 patients who had the diagnosis of definite IE at a median of 171 (53-421) days following TAVR. PEE was defined as the presence of an intracardiac abscess, pseudoaneurysm or fistula confirmed by transthoracic/transophageal echocardiography, computed tomography or peri-operative findings.

***Results**:* A total of 105 patients (18.1%) were diagnosed with PEE (perivalvular abscess, pseudoaneurysm, fistula, or a combination in 87, 7, 7, and 4 patients, respectively). A history of chronic kidney disease (OR_{adj}: 2.08; 95% CI: [1.27-3.41], p=0.003) and IE secondary to coagulase-negative staphylococci (OR_{adj}: 2.71; 95% CI: [1.57-4.69], p<0.001) was associated with an increased risk of PEE. Surgery was performed at index IE episode in 34 patients (32.4%) with PEE (*vs*. 15.2% in patients without PEE, p<0.001). In-hospital and 2-year mortality rates among PEE-IE patients were 36.5% and 69.4%, respectively. Factors independently associated with an increased mortality risk were the occurrence of other complications (stroke post-TAVR, acute renal failure, septic shock) and the lack of surgery at index IE hospitalization (p_{adj}<0.05 for all).

***Conclusion**:* PEE occurred in about one fifth of IE post-TAVR patients, with the presence of coagulase-negative staphylococci and chronic kidney disease determining an increased risk. Patients with PEE-IE exhibited very high early and late mortality rates, and surgery during IE hospitalization seemed to be associated with better outcomes.

Key words: Infective endocarditis, TAVI, TAVR, heart surgery

ABBREVIATIONS

CT : computed tomography

HF : heart failure

HR : hazard ratios

IE : infective endocarditis

OR : Odds ratio

PEE : perivalvular extension

TAVR : trans-catheter aortic valve replacement

INTRODUCTION

Infective endocarditis (IE) is a life-threatening disease, with in-hospital mortality rates ranging from 15 to 30% [1–4]. Perivalvular extension (PEE) is the most frequent cause of uncontrolled infection after IE [5], and such complication has been reported in up to one third of the patients in series including systematic transesophageal echocardiography screening [6,7]. The successful treatment of this condition relies on microbial eradication by anti-microbial drugs associated with surgery to remove the infected material.

Transcatheter aortic valve replacement (TAVR) has become the default treatment for the majority of elderly patients with aortic stenosis, and the cumulative 5-year risk of IE following TAVR has been estimated of 6% [8]. Numerous studies have evaluated the main features and outcomes of IE after TAVR [9–13], but to date no study determined the risk, clinical characteristics and outcomes of PEE in such patients. Several differential aspects of the TAVR population (older patients with a high co-morbidity burden) along with specific features related to transcatheter valves (larger amount of metal around valve leaflets compared to surgical bioprostheses) and periprocedural TAVR management and complications may influence the occurrence, characteristics and outcomes of PEE in such patients. Also, the role of surgery for the treatment of complicated IE remains to be established in TAVR recipients [14]. Thus, we sought to evaluate the rate, characteristics, management and outcomes of PEE in patients with IE following TAVR.

METHODS

Study population

Data were obtained from The Infectious Endocarditis after TAVR International Registry. Details on the design of this observational, multicenter, international registry have been previously reported [10]. At the time of this analysis, the registry included data from 579 patients with definite IE determined by the modified Duke criteria after TAVR from 59 centers in 11 countries across Europe, North America, and South America between June 2005 and November 2020. Informed consent was

obtained from all patients before the procedure and the individual anonymized data sharing was performed according to the local ethics committee of each center.

Patients were retrospectively identified by each center according to the modified Duke criteria [5]. Only TAVR patients developing definite IE were included regardless of the cardiac structure affected (native/prosthetic valve and/or implantable cardiac device). To avoid duplicities, only the first episode of IE recorded for an individual patient was included in the analysis. A dedicated uniform case report form (database) was used at all sites for data collection that included baseline and periprocedural TAVR features, as well as IE characteristics, microbiological profile, management and in-hospital and follow-up outcomes (191 variables). The global cohort was divided into two groups: patients presenting PEE during index IE hospitalization (PEE-IE), and patients without PEE during IE hospitalization (NPEE-IE).

Study definitions

The definition of definite IE was based on the modified Duke criteria [5]. PEE was defined as the presence of an intracardiac abscess, pseudoaneurysm or fistula confirmed by transthoracic, transophageal echocardiography, computed tomography images or peri-operative finding [15]. Transcatheter aortic valve type was divided into two groups: balloon-expandable (Edwards Sapien™, Sapien XT™, and Sapien 3™ valves systems; Edwards Lifesciences, Irvine, CA, USA) and self- or mechanically- expandable valve (Medtronic CoreValve™ and Evolut R™ systems [Medtronic, Minneapolis, MN], Lotus™ Valve System (Boston Scientific, Marlborough, MA, USA), Portico™ valve (Abbott Vascular, Abbott Park, IL, USA), Symetis Acurate™ valve system (Symetis SA, a Boston Scientific company, Ecublens, Switzerland), Direct flow™ (Direct Flow Medical Inc. Santa Rosa, CA, USA), JenaValve™ (JenaValve Technology Inc. Irvine, CA, USA), Medtronic Engager™(Medtronic, Minneapolis, MN, USA) and Centera™ (Edwards Lifesciences, Irvine, California, USA). Clinical endpoints were defined according to the Valve Academic Research Consortium-2 criteria [16]. Health care–associated IE was defined as previously reported [17].

Persistent bacteremia was defined as positive blood cultures despite appropriate antibiotic therapy for > 7 days. Chronic kidney disease was defined by glomerular filtration rate <60 mL/min/1.73 m2. Significant transcatheter heart valve dysfunction was defined by a new diagnosis of moderate to severe aortic regurgitation or stenosis.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the variable distribution, which was assessed using the Kolmorogov-Smirnov test. Categorical variables were expressed as number (%). Comparisons between groups were performed using the Student t test or Wilcoxon rank-sum test for continuous variables and χ2 or Fisher exact test for categorical variables. A multivariable model was performed to determine the factors associated with PEE. Baseline, TAVR-procedure, and IE episode-related variables considered a priori to contribute to PEE during IE admission were included in the multivariable model. A multivariable Cox proportional hazard model was performed to determine the factors independently associated with cumulative follow-up mortality among PEE-IE patients. Likewise, this model included all baseline, TAVR-procedure, and IE episode-related variables considered a priori to contribute to 2-year mortality among this group of patients. The variables with a *p* value <0.20 in the bivariate analysis were included in both multivariable models. Both models were built by backward stepwise (likelihood ratio) selection. The Kaplan–Meier method was used to provide survival estimates, which were assessed with a log-rank test. Event times were measured from the date of initial IE symptoms to the date of death or last follow-up. Differences in the incidence of mortality were determined using the log-rank test. A 2-sided *p* value of <0.05 was considered statistically significant. Data analyses were performed using the STATA 14.0 (StataCorp, College Station, TX, USA).

RESULTS

The study included 579 patients with a diagnosis of IE at a median time of 171 (53-421) days following TAVR. Among them, 105 (18.1%) patients presented with a PEE at index IE hospitalization. The baseline and procedural characteristics of the study population according to the occurrence of PEE are shown in **Table 1.** PEE-IE patients exhibited higher rates of chronic kidney disease (p=0.032) and previous open-heart surgery (p=0.049) compared to those without PEE.

Clinical characteristics and outcomes of PEE-IE

Among patients with PEE, 87, 7, 7, 2 and 2 patients were diagnosed with perivalvular abscess, pseudo-aneurysm, fistula, abscess plus fistula, and abscess plus pseudo-aneurysm plus fistula, respectively. PEE occurred in patients with IE located at the TAVR prosthesis (65 patients, 61.9%), the mitral valve (10 patients, 9.5%), multiple locations (25 patients, 23.8%), and right-sided heart structures (5 patients, 4.8%).

The clinical characteristics and outcomes of IE post-TAVR, according to the occurrence of PEE are shown in **Table 2**. PEE-IE patients presented more frequently with heart failure (52.4% vs. 39.7%, p=0.018) and neurological (26.0% vs. 17.0%, p=0.050) symptoms, and had larger vegetations (10 mm; 95%CI [6-15] mm vs. 12mm; 95%CI [8-17] mm, p=0.032). Coagulase-negative staphylococci were the predominant causative organism in PEE-IE patients (33 patients, 32.4%). In the multivariable analysis, chronic kidney disease (OR_{adj}: 2.08 95% CI [1.27-3.41], p=0.003) and coagulase-negative staphylococci (OR_{adj}: 2.71; 95%CI [1.57-4.69], p<0.001) associated with an increased risk of PEE **(Table 3).**

PEE-IE patients were more likely to have complications, including HF episodes (56.9% *vs*. 39.4%, p=0.001) and persistent bacteremia (45.2% *vs*. 27.0%, p<0.001) during index hospitalization, and exhibited a higher rate of surgical intervention (32.4% *vs*. 15.2%, p<0.001). There were no

differences between groups regarding in-hospital mortality (PEE-IE: 36.5% *vs*. NPEE-IE: 32.3%, *p*=0.41).

The Kaplan-Meier survival curves at 2-year follow-up according to the occurrence of PEE at index IE hospitalization are shown in **Figure 1**. At 2-year follow-up, PEE-IE patients exhibited a higher all-cause mortality rate (69.4%, 95% CI[59.0-79.3]) compared to NPEE-IE patients (53.7%; 95% CI [48.9-58.7], *p*=0.028).

The analysis of the factors associated with an increased all-cause mortality risk among PEE-IE patients is shown in **Table 4**. In the multivariable analysis, stroke after TAVR (HR_{adj}: 4.78, 95% CI: [1.55-14.7], *p*=0.006), acute renal failure (HR_{adj}:2.18, 95%CI: [1.15-4.13], *p*=0.017), septic shock (HR_{adj}: 3.12, 95%CI: [1.63-6.00], *p*=0.001), and the lack of surgery (HR_{adj}: 1.93, 95%CI: [1.02-3.67], *p*=0.045) during the IE hospitalization were associated with increased mortality.

Surgical intervention in PEE-IE patients

Among PEE-IE patients, those who had a surgical intervention at the index IE episode (n=34) had similar baseline characteristics compared to those with no intervention, except for a higher rate of chronic kidney disease (61.4% *vs*. 35.3%, *p*=0.021) and acute renal failure after TAVR (16.9% *vs*. 0.0%, *p*=0.008) (**Supplementary Table 1**). The *Staphylococcus aureus* was more frequently the cause of IE among PEE-IE patients without surgery (29.4% *vs*. 5.9%, *p*=0.009), but there were no differences regarding in-hospital complications between surgically and no-surgically managed patients (**Supplementary Table 1**). A total of 8/34 patients (23.5%) died after surgery, but in-hospital mortality tended to be lower among surgically managed patients compared to their non-surgically managed counterparts (42%, *p*=0.082).

Sub-analysis of the population with IE located only at the TAVR prosthesis

A total of 284 patients (49.1%) had an infection located exclusively at the TAVR prosthesis, and of them, 65 (22.9%) presented with PEE. The clinical characteristics and outcomes of patients with IE located exclusively at the TAVR prosthesis according to the occurrence of PEE are shown in **Supplementary Table 2**. PEE-IE patients had higher rates of HF episodes (58.1% *vs*. 38.7%, *p*=0.008), septic shock (41.7% *vs*. 23.7%, *p*=0.009), and persistent bacteremia (45.6% *vs*. 27.7%, *p*=0.015). A surgical intervention at index IE episode was more frequently performed in PEE-IE patients (38.5% *vs*. 16.4%, *p*<0.001), and in-hospital mortality was higher in PEE-IE patients (40.6% *vs*. 27.7%, *p*=0.006). At 2-year follow-up, the mortality rate was 64.4% 95%CI: [51.2 -77.4] in PEE-IE patients *vs*. 48.1% 95%CI: [41.2 -55.5] in NPEE-IE patients (*p*=0.021). The clinical characteristics of patients with PEE and TAVR prosthesis involvement only *vs*. other localization of IE (including the TAVR prosthesis) are available in **Supplementary Table 3.** Causative microorganism were different since coagulase-negative staphylococci where more frequently found in other locations (47.4% *vs*. 22.6%, *p*=0.009) whereas enterococci where predominant in patients with TAVR involvement (30.7% *vs*. 12.5%, *p*=0.035). In the PEE subgroup with TAVR only involvement, 60.32% of patients had no TAVR dysfunction, 28.57% had moderate to severe aortic regurgitation, 9.52% had moderate to severe stenosis and 1.59% had both stenosis and regurgitation. In patients with PEE, the mortality rate was similar in patients with TAVR involvement only compared to other locations (*p*=0.840).

DISCUSSION

The main findings of this multicentre international study involving 59 centres and describing IE after TAVR in 579 patients are: (i) PEE was observed in about one fifth of patients following TAVR, (ii) patients with staphylococcus coagulase-negative and those with chronic kidney disease were at higher risk to develop PEE, (iii) the occurrence of PEE was associated with higher mortality rates at 2 years, and (iv) only one third of PEE-IE patients received surgical treatment, which was indeed associated with improved outcomes.

Rate of perivalvular extension

PEE was a common complication affecting 18.1% of patients in our cohort. Interestingly, this rate was lower than previous studies focusing on PEE in non-TAVR patients describing this complication in about 32 to 37% of cases [6,7]. However, larger IE international cohorts including native valve IE showed roughly similar rates than our study, ranging between 11.6% and 23.4% [18–20]. This discrepancy may be related to a more accurate screening of patients with systematic multimodal imaging. In fact, IE is a complex disease with challenges in the detection of both cardiac and extra-cardiac lesions secondary to the infection. The extension of the disease in adjacent tissues or other organs have important implications in the management of patients. Therefore, following transthoracic echocardiography, other imaging modalities including transesophageal echocardiography, cardiac computed tomography, fluoro-18-fluorodeoxyglucose positron tomography or radiolabeled leucocyte scintigraphy are mandatory [21]. TAVR bioprosthesis have a large amount of metal causing different motion artifact and the shape of some prostheses extending into the ascending aorta may pose difficulties in visualizing the entire implant. These particular characteristics would emphasize the critical need of an exhaustive multimodality assessment of IE post-TAVR patients. ECG-gated computed tomography (CT) is a useful tool to visualize the anatomy of abscess, pseudo-aneurysm and fistulae [22]. Even if CT has a lower specificity compared to transesophageal echocardiography to diagnose PEE [23], it is a highly sensitive imaging method (100% of sensitivity) compared to intraoperative findings [24,25]. In the EuroENDO registry, abscess was only present in 11.6% of the population. However, when analyzing the population with CT, PEE was present in 33.7% overall and 48.6% of patients with a prosthetic valve. Thus, systematic additional investigations including ECG-gated CT may be warranted in IE post-TAVR patients due to the important management and prognostic implications of this complication.

Risks factors

Graupner et al. found that a former IE episode, the presence of a prosthetic valve, aortic location and coagulase-negative staphylococci were associated with the occurrence of PEE in non-TAVR patients with IE [7]. This finding was later confirmed by an international cohort of patients with prosthetic valve endocarditis [26]. Indeed, Chu et al. found higher rates of intracardiac abscess in coagulase-negative patients (38%) compared to patients with either *Staphylococcus aureus* (23%, p=0.03) or viridans streptococci (20%, p=0.05) infection. Our study also confirms this association in IE after TAVR. Coagulase-negative staphylococci are an invariable constituent of the normal skin flora. A higher rate of IE related to this organism in health care exposure patients has been previously reported [27]. The virulence of different coagulase-negative species is inconsistent. *Staphylococcus lugdunensis* has been reported to be very aggressive with poor prognosis [28]. Unfortunately, identification of coagulase-negative strains to the species level was not reported by participating centers and the rate of each species was not evaluated in our study. Therefore, further studies are warranted to completely understand the particular pathogenicity of coagulase-negative staphylococci individual species in the occurrence of PEE.

Interestingly, chronic kidney disease was also found to be a predictive factor of PEE. It is well established that patients with renal impairment are at higher risk to develop infectious diseases [29]. This vulnerability is related to a multifactorial impaired immune system with reduced lymphocyte production, leukocytes and neutrophil dysfunction, inappropriate inflammatory signals, and comorbidities associated with immunodepression [30].

These results highlight the importance of these two risks factors, coagulase-negative staphylococci and chronic kidney disease, in the occurrence of PEE. Therefore, the presence of these factors in a confirmed case of IE should be taken into account and trigger complementary investigations to facilitate diagnosis of PEE.

Clinical course

The occurrence of PEE is associated with a very high mortality rate, and the occurrence of this complication has been considered an indication for surgery [5]. However, IE series in non-TAVR recipients showed that the mortality rate may remain high among PEE-IE patients despite surgical treatment (up to 41% in a study reporting outcomes of 76 patients of whom 87% had surgery) [31]. In our study, only 32.4% of patients had surgery in the subgroup with PEE, leading to a mortality rate in this group of 8.8% at one month, 50.0% at one year and 70.0% at two years. Surgical therapy is usually performed in ~~about~~ 39.0% to 48.2% of IE cases in large registries [2,32–34], whereas only 17.4% of our whole population had surgery. This discrepancy seems to be related to the fear of periprocedural surgical complications and post-operative death of this elderly and highly comorbid population that had previously been deemed better candidates for non-transcatheter intervention. Our study showed that PEE-IE patients who underwent surgery appeared to have similar comorbidity and in-hospital complications rates compared to their non-surgically managed counterparts but residual confounding factors may have not been taken into account. It seems therefore that the surgical decision was based on individual risk assessment evaluated by clinical factors and medical judgement not captured by our investigation.

Surgery seemed to be an independent protective factor in the multivariable analysis. This finding is of potential interest particularly in the actual context where TAVR is expanding towards the treatment of lower surgical risk patients. Nevertheless, residual confounding factors may have not be taken into account and the low number of patients along with the design of this study do not allow us to draw definitive conclusions about the potential benefit of surgery. Interestingly, despite the high rate of death in the PEE group, few patients treated medically survived at two years. This may be related to the surprisingly low number of patients with significant TAVR dysfunction (60.32%). Thus long term medical treatment in selected patients inadequate for surgery and with little hemodynamic impairment may be an option [35]. Further studies are warranted to confirm the potential benefit of surgery in IE patients with PEE after TAVR and to precise which patient would benefit the more.

Study limitations

Our study has some limitations. First, due to its retrospective observational design, some data were not available. For instance, we did not gather information about imaging modalities used to define each diagnosis, particularly regarding PEE. Centers participated voluntarily and there was no external monitoring committee to verify the accuracy of data reported by each center. Second, species identification of coagulase-negative bacteria was not reported and comprehensive data cannot be provided. Third, the multivariate analysis of factors associated with death in patients with PEE may be hampered by the low number of events in this sub-population and these results should therefore be interpreted with caution. Furthermore, PEE may have been diagnosed during the surgical procedure posing a risk of classification bias. The long study period (from 2005 to 2020) has potentially led to historical biases. Also, the definition of health care associated EI may have not taken into account periprocedural cases with delayed manifestation. Lastly, due to its multicentre design, diagnosis and treatment modalities of patients may have been different between participating centres.

CONCLUSION

In this large registry of IE after TAVR, about one out of five patients complicated with PEE, and this complication was associated with high early and midterm mortality rates. Coagulase-negative staphylococci and chronic kidney disease determined an increased risk of suffering this complication. Surgical treatment was implemented in a minority (about one third) of IE-PEE patients, and the lack of surgery seemed to be associated with poorer outcomes.

NOTES

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CONFLICT OF INTEREST

Josep Rodés-Cabau has received institutional research grants from Edwards Lifesciences, Medtronic, and Boston Scientific. Vassili Panagides has received received institutional research grants from Medtronic, Boston scientific and Microport.Didier Tchetche has reported consulting fees from Abbott Vascular, Boston Scientific, Edwards Lifesciences, and Medtronic. Howard C. Herrmann has received institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences and Medtronic and consulting fees from Edwards Lifesciences and Medtronic. John G Webb has reported that he has received consulting fees from Edwards Lifesciences and St Jude Medical. Raj Makkar has reported that he has received research grants from Edwards Lifesciences, Medtronic, Abbott, Capricor, and St Jude Medical; has served as a proctor for Edwards Lifesciences; and has received consulting fees from Medtronic. Fabio Sandoli de Brito Jr. has reported that he has received honoraria from Medtronic and Edwards Lifesciences for symposium sPEEches and proctoring cases. Stamatios Lerakis has reported that he has received consulting fees from Edwards Lifesciences. Hervé Le Breton reports lecture fees from Edwards Lifesciences, outside the submitted work. Jan Malte Sinning

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Table 1 : Baseline characteristics of patients with and without perivalvular extension

	Without perivalvular extension (n=474)	With perivalvular extension (n=105)	Unadjusted *p-value*
Baseline characteristics			
Age, years ± SD	78.8 ± 7.7	78.3 ± 6.6	0.494
Male, n (%)	292 (61.6)	70 (66.7)	0.332
Body mass index (kg/m2)	26.9 (23.9-30.7)	27.3 (24.3-30.1)	0.763
Diabetes mellitus, n (%)	177 (37.3)	39 (37.1)	0.970
Chronic obstructive pulmonary disease, n (%)	129 (27.2)	29 (27.6)	0.933
Atrial fibrillation, n (%)	207 (43.8)	40 (38.1)	0.288
Chronic kidney disease, n (%)	193 (41.3)	55 (52.9)	**0.032**
Previous Stroke, n (%)	61 (12.9)	14 (13.3)	0.898
Previous open-heart surgery, n (%)	98 (20.7)	31 (29.5)	**0.049**
Previous valve surgery, n (%)	50 (10.6)	12 (11.4)	0.803
Previous infectious endocarditis, n (%)	5 (1.1)	1 (1.0)	1.00

Logistic EuroSCORE, % (SD)	14.0 (8.7-23.4)	12.8 (7.6-21.0)	0.284
Left ventricular ejection fraction, % ± SD	53.8 ± 13.4	52.5 ± 12.9	0.379
Mean transaortic gradient, mean ± SD, mmHg	45.1 ± 16.1	45.6 ± 14.8	0.802
Periprocedural characteristics			
Implantation site			
Catheterization laboratory, n (%)	193 (40.7)	41 (39.0)	0.793
Operating hybrid room, n (%)	28 (5.9)	8 (7.6)	
Hybrid room	253 (53.4)	56 (53.3)	
Approach, n (%)			
Transfemoral	421 (89.2)	87 (82.9)	0.070
Prosthesis type			
Balloon-expandable, n (%)	241 (51.8)	57 (54.3)	0.649
Self-expanding, n (%)	233(48.2)	48 (45.7)	
Antibiotic prophylaxis			
B-Lactam alone, n (%)	393 (94.0)	85 (92.4)	0.657
Vancomycin alone or in combination, n (%)	16 (3.8)	4 (4.3)	

Other	9 (2.2)	3 (3.3)	
In-hospital Outcomes after TAVR insertion			
Acute renal failure, n (%)	62 (13.4)	12 (11.4)	0.579
Stroke, n (%)	23 (5.0)	4 (3.8)	0.609
Major vascular complication, n (%)	32 (6.9)	6 (5.7)	0.650
Major bleeding, n (%)	44 (9.5)	10 (9.5)	0.994
Sepsis, n (%)	50 (11.8)	6 (6.0)	0.089
New pacemaker implantation, n (%)	91 (19.4)	14 (13.3)	0.153
Residual aortic regurgitation >2 at discharge, n (%)	69 (15.0)	13 (12.5)	0.509
Mean residual transaortic gradient, mean ± SD, mm Hg	10.9 ± 6.0	12.3 ± 8.5	0.115
Length of hospital stay, median [IQR], days	9.0[6.0-15.0]	9.0[6.0-13.5]	0.447

Table 2 : Main clinical characteristics, management, and outcomes of IE after TAVR in patients with and without peri-valvular extension

	Without perivalvular extension (n=474)	With perivalvular extension (n=105)	Unadjusted *p*-value
Time from TAVR, median (IQR), days	174.0[45.0-425.0]	164.0[63.0-367.0]	0.689
Initial symptoms			
Fever, n (%)	360 (78.3)	84 (80.0)	0.695
New-onset heart failure, n (%)	182 (39.7)	55 (52.4)	**0.018**
Neurological, n (%)	78 (17.0)	27 (26.0)	**0.035**
Systemic embolism, n (%)	59 (12.9)	14 (13.5)	0.874
Skin lesions	21 (4.6)	4 (3.8)	0.999
Health care–associated infection, n (%)	213 (44.9)	37 (35.2)	0.070
Echocardiographic findings, No./total (%)			
Valves involved			
TAVR prosthesis alone, n (%)	219/474 (46.2)	65/105 (61.9)	**0.032**

Mitral (native or prosthetic valve), n (%)	76/474 (16.0)	10/105 (9.5)	
Multiple localization, n (%)	152/474 (32.1)	25/105 (23.8)	
Right sided endocarditis alone, n (%)	27/474 (5.7)	5/105 (4.8)	
Vegetation size, mm, median [IQR]	10 [6-15]	12 [8-17]	**0.032**
Significant TAVR dysfunction			
None, n (%)	317/383 (82.8)	70/103 (68.0)	**0.004**
Regurgitation, n (%)	42/383 (11.0)	25/103 (24.3)	
Stenosis, n (%)	19/383 (5.0)	7/103 (6.8)	
Both, n (%)	5/383 (1.3)	1/103 (1.0)	
Causative microorganisms, No./total (%)			
Staphylococcus aureus, n (%)	115/451 (25.5)	22/102 (21.6)	0.406
Methicillin-resistant	20/115 (17.4)	5/22 (22.7)	0.553
Coagulase-negative Staphylococci, n (%)	64/451 (14.2)	33/102 (32.4)	**<0.001**
Methicillin-resistant	20/64 (31.3)	8/33 (24.2)	0.637
Enterococci, n (%)	119/451 (26.4)	24/102 (23.5)	0.552
Streptococci			

S. viridans, n (%)	62/451 (13.7)	9/102 (8.8)	0.179
Bovis group Streptococci, n(%)	26/451 (5.8)	0/102 (0)	**0.008**
Others, n (%)	18/451 (4.0)	4/102 (3.9)	0.999
Culture negative, n (%)	29/452 (6.4)	6/102 (5.9)	0.841
Presumed source of entry, n (%)			
Unknown, n (%)	159 (34.4)	47 (45.6)	
Procedural TAVR related, n (%)	22 (4.8)	5 (4.9)	
Urological, n (%)	46 (10.0)	5 (4.9)	
Odontological, n (%)	18 (3.9)	1 (1.0)	
Pacemaker implantation, n (%)	9 (1.9)	3 (2.9)	0.202
Skin/soft tissue infection, n (%)	15 (3.2)	4 (3.9)	
Digestive, n (%)	32 (6.9)	6 (5.8)	
Cancer, n (%)	3 (0.6)	2 (1.9)	
Other, n (%)	109 (26.4)	25 (26.3)	
Complications during IE hospitalization No./total (%)			
Heart failure, n (%)	177/449 (39.4)	58/102 (56.9)	**0.001**
Acute renal failure, n (%)	173/416 (41.6)	41/97 (42.3)	0.902

Septic shock, n (%)	121/448 (27.0)	34/100 (34.0)	0.161
Stroke, n (%)	45/449 (10.0)	12/102 (11.8)	0.602
Systemic embolization, n (%)	48/448 (10.7)	10/101 (9.9)	0.810
Persistent bacteremia, n (%)	106/392 (27.0)	42.93 (45.2)	**<0.001**
Management and Outcomes, n (%)			
Antibiotic treatment alone, n (%)	400 (84.7)	71 (67.9)	**<0.001**
Antibiotic + Surgery during IE hospitalization, n (%)	70 (15.2)	34 (32.4)	
Time to surgery, median [IQR], days	17.5 [4.5-36.0]	14 [8-41]	0.538
Transcatheter valve in valve, n (%)	3 (1.5)	0 (0)	0.999
Isolated pacemaker extraction, n (%)	8 (4.0)	0 (0)	0.357
In-hospital mortality, n (%)	150 (32.3)	38 (36.5)	0.410

Table 3 – Univariate and multivariate analysis of risks factors associated with PVE

	Univariate Analysis		Multivariate Analysis	
	Odds ratios (95% CI)	Unadjusted p Value	Odds Ratio (95% CI)	Adjusted p Value
Baseline characteristics				
Chronic kidney disease	1.59 [1.04-2.44]	**0.032**	2.08 [1.27-3.41]	**0.003**
Previous heart surgery	1.61 [1.00-2.58]	0.055		
Periprocedural characteristics				
Transfemoral approach	0.59 [0.33-1.05]	0.082		
In-hospital Outcomes (TAVR)				
Sepsis	0.47 [0.20-1.14]	0.071		
New pacemaker implantation	0.64 [0.35-1.18]	0.140		
Mean residual transaortic gradient	1.03 [1.00-1.07]	0.052		
Causative micro-organism				
Coagulase-negative Staphylococci	2.89 [1.77-4.73]	**<0.001**	2.72 [1.57-4.69]	**<0.001**
S. Viridans	0.60 [0.29-1.27]	0.162		

Table 4 : Univariate and multivariate analysis of parameters associated with all-cause mortality in patients with peri-valvular extension

	Univariate Analysis Hazard Ratio (95% CI)	Unadjusted p Value	Multivariate Analysis Hazard Ratio (95% CI)	Adjusted p Value
In-hospital Outcomes (TAVR)				
Transfemoral access	0.64 [0.34-1.18]	0.17	0.63 [0.32-1.22]	0.170
Acute renal failure	1.60 [0.81-3.16]	0.195		
Stroke	4.77 [1.66-13.71]	**0.016**	4.78 [1.55-14.7]	**0.006**
Residual aortic regurgitation >2 at discharge	1.85 [0.98-3.47]	0.07		
IE clinical features				
Neurological symptoms at admission	2.29 [1.35-3.86]	**0.003**		
Health care-associated infection	1.40 [0.85-2.31]	0.188		
In-hospital complication during IE				
Heart failure	1.88 [1.09-3.25]	0.019		
Acute renal failure	3.27 [1.92-5.58]	**<0.001**	2.18 [1.15-4.13]	**0.017**

Septic Shock	3.92 [2.32-6.60]	<0.001	3.12 [1.63-6.00]	**0.001**
Stroke	1.87 [0.95-3.73]	0.09		
Persistent bacteremia	1.88 [1.20-3.23)	0.022		
Management				
Surgery at index IE hospitalization	0.66 [0.38-1.16]	0.138	0.52 [0.27-0.98]	**0.045**

FIGURE TITLE AND LEGENDS

Figure 1:

Kaplan-Meier curves comparing survival stratified into PEE and NPEE. Test comparing the two groups was based on the log-rank test

Figure 1