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RESEARCH ARTICLE

Incidence, Clinical Characteristics, and Impact of Absent Echocardiographic Signs in Patients with Infective Endocarditis after Transcatheter Aortic Valve Implantation

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Background: Echocardiography is the primary imaging modality for diagnosis of infective endocarditis (IE) in prosthetic valve endocarditis (PVE) including IE after transcatheter aortic valve implantation (TAVI). This study aimed to evaluate the characteristics and clinical outcomes of patients with absent compared with evident echocardiographic signs of TAVI-IE.

Methods: Patients with definite TAVI-IE derived from the *Infectious Endocarditis after TAVI International Registry* were investigated comparing those with absent and evident echocardiographic signs of IE defined as vegetation, abscess, pseudoaneurysm, intracardiac fistula or valvular perforation or aneurysm.

Results: Among 578 patients, 87 (15.1%) and 491 (84.9%) had absent (IE-neg) and evident (IE-pos) echocardiographic signs of IE, respectively. IE-neg were more often treated via a transfemoral access with a self-expanding device, and had higher rates for peri-interventional complications (e.g. stroke, major vascular complications) during the TAVI procedure ($p < 0.05$ for all). IE-neg had higher rates of IE caused by *staphylococcus aureus* (33.7% vs. 23.2%, $p = 0.038$) and *enterococci* (37.2% vs. 23.8%, $p = 0.009$), but lower rates of coagulase-negative *staphylococci* (4.7% vs. 20.0%, $p = 0.001$).

IE-neg was associated with the same dismal prognosis for in-hospital mortality in a multivariate binary regression analysis (OR 1.51, 95%-CI 0.55-4.12) as well as a for 1-year mortality in a Cox regression analysis (HR 1.10, 95%-CI 0.67-1.80).

Conclusions: Even with negative echocardiographic imaging, patients who have undergone TAVI and presenting with positive blood cultures and symptoms of infection are a high-risk patient group having a reasonable suspicion of IE and the need for an early treatment initiation.

Key words: TAVI, infective endocarditis, imaging, TEE, Duke criteria

ABBREVIATIONS:

IE-neg – infective endocarditis with absent echocardiographic signs

IE-PV – infective endocarditis treated with evident echocardiographic signs

PVE – prosthetic valve endocarditis

TAVI – transcatheter aortic valve implantation

TEE – transesophageal echocardiography

¹⁸F-FDG PET – ¹⁸F-fluorodeoxyglucose positron emission tomography

WBC SPECT/CT – white blood cell single-photon emission computed tomography/computed tomography

INTRODUCTION

The incidence of infective endocarditis after transcatheter aortic valve implantation (TAVI-IE) ranges between 0.7% and 3.4% per patient-year [1-7] and its prognosis is poor irrespective of initial treatment. [8]. Therefore, an early diagnosis, besides preventive measures, appears to be of utmost importance to impact the prognosis of patients with suspected TAVI-IE.

Echocardiography has a key role in the diagnosis of IE and the prediction of embolic risk. Moreover, echocardiography is also crucial for prognostic assessment, follow up under therapy and during the perioperative phase. According to European guidelines, transesophageal echocardiography (TEE) is the imaging modality of choice for diagnosing infective endocarditis (IE) in prosthetic valve endocarditis (PVE). [9] However, negative echocardiography findings may be observed in about 15% of cases of IE. [10] The most frequent explanations for negative echocardiography are very small or absent vegetations and difficulties in identifying vegetations in the presence of pre-existent conditions, e.g. prosthetic heart valve. Both TEE and Duke criteria have a reduced sensitivity and specificity in PVE [9], and this is particularly true for TAVI-IE. [11] This is mainly due to the challenging imaging situation with the acoustic shadowing of the stented frame abutting the native valve leaflets leading to negative imaging in one third of patients with TAVI-IE. [3, 7] These distinctive features of TAVI-IE can delay diagnosis and therapy and have even led to postmortem diagnosis only. [12] Recent studies have shown that ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG PET) uptake around surgical valves is an accurate indicator of PVE and case series described its applicability in TAVI-IE. [11] However, there are no systematic and large scale data for computed tomography (CT) or ¹⁸F-FDG PET evaluation in patients with suspected TAVI-IE. Thus, the aim of this analysis derived from the *Infectious Endocarditis after TAVI International Registry* was to evaluate the characteristics and clinical outcomes of patients with absent compared with evident echocardiographic signs of TAVI-IE and to describe the utilization of nuclear imaging modalities in the setting of TAVI-IE.

METHODS

The Infectious Endocarditis after TAVI International Registry

The data underlying this article will be shared on reasonable request to the corresponding author and participating investigators. Details regarding the design of the observational, multicenter, international *Infectious Endocarditis after TAVI International Registry* have been published

previously. [7] Briefly, the registry collected data from 604 patients with definite IE according to the modified Duke criteria after TAVI from 59 TAVI 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.

Patient selection and data collection

Patients were retro- and prospectively identified by each center according to the modified Duke criteria. TAVI patients with definite IE were included irrespective of the structure affected (prosthetic/native valve and/or implantable cardiac device and/or no echocardiographic signs in patients with continuous bacteremia and at least two other minor criteria according to the modified Duke criteria). Only the first IE episode recorded for an individual patient was included in the analysis, thereby avoiding duplicities. At each site, a dedicated case report form was used for data collection.

Based on transesophageal echocardiography, the global cohort was divided into IE-neg and IE-pos with data available in 578 patients.

Definitions

The definition of definite IE was based on the modified Duke criteria. [13] Clinical endpoints were defined according to the Valve Academic Research Consortium-2 criteria. [14] IE-pos was defined as the single presence or combination of vegetation, abscess, pseudoaneurysm, intracardiac fistula or valvular perforation/aneurysm detected by echocardiography. Perioperative mortality risk was defined according to the logistic EuroSCORE I. [15] Transcatheter aortic valve type was divided into two groups: balloon-expandable and self- or mechanically-expandable valves. IE with TAVI platform affection was defined as any IE episode involving the TAVI prosthesis (leaflet and/or stent frame). Early IE was defined as occurring within 1 year, late IE >1 year following TAVI. [9] Health care-associated infection was defined as IE diagnosed within 48 hours of admission in an outpatient with extensive health care contact as previously described. [16] Periannular complications, persistent bacteremia and systemic embolization were defined as previously reported. [7]

Outcome measures

The 1-year all-cause mortality after symptom onset was the primary outcome measure. In-hospital and 2-year mortality was a secondary outcome measure. Long-term follow-up was complete in 98.3% (11 patients were lost to follow-up at 1 year, all in IE-pos). The complications during IE treatment were collected and included heart failure, acute renal failure, stroke, septic shock, systemic embolization, persistent bacteremia, and the composite of those complications.

Statistical analysis

Continuous variables were expressed as mean \pm standard deviation or median (interquartile range) depending on the variable distribution, which was assessed using the Kolmogorov-Smirnov test. Categorical variables were expressed as numbers (%). Group comparison between groups was analyzed using the Student t test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact test for categorical variables. Unadjusted hazard ratios were computed using a univariate Cox proportional hazards model. To evaluate the factors associated with mortality among patients with TAVI-IE, Cox proportional hazards models were fit for all-cause 1-year mortality. These models included all clinical relevant variables considered a priori to contribute to mortality. Multivariable cox regression model was performed including all variables with $p < 0.1$ in the univariable model. To estimate factors associated with in-hospital mortality, univariable and multivariable logistic regressions including all variables with $p < 0.1$ in the univariable model were performed. We used the Kaplan–Meier method to provide survival estimates with differences assessed by the log-rank test in the crude cohort. Moreover, we performed sensitivity analyses by excluding patients without TAVI prosthesis involvement in IE-pos and patients with positive nuclear imaging in IE-neg with regard to in-hospital, 1-year, and overall mortality. 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 < 0.05 was considered statistically significant. Data analyses were performed using the Stata software (version 15.1, Stata Corp, College Station, TX, USA).

RESULTS

Baseline and TAVI characteristics

Among 578 TAVI-IE patients, 87 (15.1%) and 491 (84.9%) were in the IE-pos and IE-neg groups, respectively.

Baseline and procedural TAVI characteristics comparing IE-neg with IE-pos are shown in *Table 1*. The groups were comparable with regard to age and sex, However, IE-neg tended to have a higher surgical baseline risk indicated by the logistic EuroScore, had lower rates of an accompanying mitral regurgitation at baseline, were more often treated via a transfemoral access with a self-expanding device, and had higher rates for peri-interventional complications (e.g. stroke, major vascular complications) during the TAVI procedure leading to a longer initial hospital stay ($p < 0.05$ for all).

Clinical characteristics, microbiology, and complications of IE

Clinical characteristics, echocardiographic features, microbiological findings, and complications during the IE episode are shown in *Table 2*. In IE-pos, the rate of very early IE (i.e. within one month) was higher than in IE-neg. Clinical presentation was not different with regard to fever,

new-onset heart failure, embolic events and skin lesion. By the design of this analysis, echocardiographic features of IE were only found in IE-pos. IE-neg had higher rates of IE caused by *staphylococcus aureus* and *enterococci* but lower rates of coagulase-negative *staphylococci*. There were no culture-negative IE cases in IE-neg.

Complications during IE treatment including heart failure, acute renal failure, septic shock, embolic complications, and persistent bacteremia were comparable between groups.

By definition, there were no typical echocardiographic findings in IE-neg. Moreover, compared to post-implantation, we found no significant overall increase in the gradients above the prostheses, but the rate of patients presenting with an increase of the mean gradient ≥ 5 mmHg was higher in IE-pos compared with IE-neg. The rate of new at least moderate aortic valve regurgitation was low and comparable between groups, whereas the rate of new at least moderate mitral regurgitation was higher in IE-pos compared with IE-neg (*Table 2*).

Therapeutic management and outcome

The management and outcomes are shown in *Table 2*. Rates of surgical treatment were significantly lower in IE-neg compared with IE-pos and nearly 97% of the IE-neg patients were treated with antibiotics alone. The in-hospital mortality rate was 40.2% in IE-neg and 31.7% in IE-pos, respectively ($p=0.118$). The follow-up for patients surviving the initial treatment period was comparable between IE-neg and IE-pos. After 1 year, mortality rates were 54.2% (95%-CI 43.8-65.4) in IE-neg and 48.2% (95%-CI 43.7-53.0) in IE-pos, respectively ($p=0.154$) (*Figure 1*).

IE-neg, compared with IE-pos, was associated with the same dismal prognosis for in-hospital mortality in a multivariate binary regression analysis (*Table 3*) as well as a for 1-year mortality in a Cox regression analysis (*Table 4*). Factors independently associated with in-hospital and 1-year mortality are provided in *Table 3* and *4* and are mainly related to complications during IE treatment.

Application of nuclear imaging

Data on the application of ^{18}F -FDG PET and WBC SPECT/CT were available in 40 (46%) of IE-neg patients and 220 (45%) of IE-pos patients. In those patients, ^{18}F -FDG PET or WBC SPECT/CT was applied in 25% of IE-neg and 15.5% of IE-pos with a predominant use of ^{18}F -FDG PET in both cohorts.

Evidence of radiolabeled tracer uptake was found in 50% of IE-neg and in 82.4% of IE-pos patients. The detailed description of those findings is given in *Table 5*.

Sensitivity analysis

Including only patients with clear TAVI prosthesis involvement in IE-pos and comparing them to IE-neg revealed similar results with regard to in-hospital, 1-year and overall mortality as in the

whole cohort. Moreover, excluding patients with positive nuclear imaging in IE-neg and comparing them with IE-pos provided consistent results. (*Supplementary Appendix*)

DISCUSSION

This study evaluated the impact of absent echocardiographic signs in TAVI-IE. The main findings can be summarized as follows: (1) About 15% of patients diagnosed with TAVI-IE according to the modified Duke criteria have no typical echocardiographic features like vegetations or perivalvular complications. (2) IE-neg had higher rates of *staphylococcus aureus* and *enterococci* compared with IE-pos. (3) Multimodality imaging was used only in a minority of patients. (4) In IE-neg, treatment was almost exclusively a conservative medical approach. (5). In-hospital and 1-year mortality in IE-neg was as high as for IE-pos.

The prognosis of patients developing IE after TAVI is poor [7] and even surgical treatment in current TAVI-IE patients does not improve 1-year mortality. [8, 17] Therefore, prevention and early diagnosis might provide the largest effect on prognosis improvement. The latter one is based on the modified Duke criteria. [13] However, PVE is typically more difficult to diagnose than native valve IE, and the modified Duke criteria have lower sensitivity and specificity in this setting due to unclear echocardiographic findings and a higher incidence of negative blood cultures. [18] In TAVI-IE, the combined sensitivity of transthoracic and transesophageal echocardiography is 67.6% (95% CI 61.7% to 73.5%) compared with 86% (95% CI 77% to 92%) in conventional PVE [19], potentially leading to delayed diagnosis and treatment. In PVE, it has been proposed to add 2 minor criteria (new-onset heart failure and presence of conduction disturbances) to improve the diagnostic sensitivity of the Duke criteria. [18] This has not been tested in TAVI-IE. The high incidence of new-onset heart failure in TAVI-IE, which was about 40% in our cohort, could support this approach.

Echocardiography in TAVI-IE. Imaging is challenging in TAVI-IE due to the acoustic shadowing of the stented frame abutting the native valve leaflets. This could be one reason why negative imaging is found in about one third of patients with TAVI-IE. (3, 7) Moreover, in our analysis IE-neg was more frequent among self-expanding prostheses recipients, likely due to the larger stent frames preventing adequate imaging. The most frequent echocardiographic findings in TAVI-IE are vegetation(s) affecting the prosthetic valve leaflets, but lesions have also been detected on the stent frame and native mitral valve. [7] There appears to be a difference between balloon-expandable and self-expanding prostheses regarding vegetation localization. Vegetations anchored to the stent frame were more often found in IE affecting self-expanding prostheses, whereas a higher rate of vegetation at the valve-leaflet level was found in IE affecting balloon-expandable valves. [20] This different localization may have contributed to the higher rate of stroke and systemic embolism in patients developing IE after balloon-expandable valves. [20] Periannular complications occur in one-fifth of TAVI-IE and are associated with a worse

outcome. [21] In contrast, the rate of new AR is relatively rare [7], whereas a significant rate of new-onset mitral regurgitation has been reported in TAVI-IE. [22] A recent publication suggested a new echocardiographic TAVI-IE phenotype, characterized by TAVI leaflet thickening and an elevated transvalvular gradient. [23] While that study was of small size, it was supported by other reports [1] and the findings of our analysis, where an increase of the mean gradient ≥ 5 mmHg was found in roughly one quarter of all patients. However, this increase was more frequent in IE-pos than in IE-neg. Nevertheless, increased gradients combined with positive blood cultures and other minor criteria of IE should raise suspicion for further diagnosis and therapy of TAVI-IE. The diagnostic impact of increased gradients included into Duke criteria and a multimodality imaging approach warrants further evaluation.

Finally, intracardiac echocardiography (ICE) might help to overcome some of the mentioned imaging difficulties and was examined in two small Danish cohorts including patients with suspected PVE and TAVI-IE but negative TEE. [5, 24] Interestingly, ICE changed the diagnosis to definite PVE in half of the patients, with a low frequency of relapse among patients in whom PVE could not be confirmed by ICE.

Multimodality imaging in TAVI-IE. A hybrid imaging approach using multislice computed tomography (MSCT), positron emission tomography (^{18}F -FDG PET) or white blood cell single-photon emission computed tomography (WBC SPECT/CT) is supported by the European Society of Cardiology (ESC) guidelines for the diagnosis of PVE. [9] The addition of ^{18}F -FDG PET increases the sensitivity of the modified Duke criteria in PVE from 52% to 90.7%, with a rise in negative predictive value from 59.7% to 87.9. [25] Concerns have been raised about using ^{18}F -FDG PET to distinguish active infection from a sterile, post-operative inflammatory response with specificity of the modified Duke falling slightly from 94.7% to 89.5% when ^{18}F -FDG PET is incorporated. [25]

Emerging data also support a specific role in TAVI-IE [23]; however, its diagnostic impact still needs to be determined in larger cohorts. In particular, the distinction between infection and post-operative inflammatory response needs to be investigated. One small study suggests that approximately 23% of patients without endocarditis exhibit tracer uptake 1 month after the procedure; however, the FDG uptake pattern can be easily differentiated between non-infected (circumferential or hemi-circumferential) and confirmed cases of TAVI-IE (focal or multifocal). [26] Another prospective study including 22 patients with non-infected transcatheter aortic valves did not exhibit a significant ^{18}F -FDG uptake pattern 3 months after the TAVI procedure with no differences between balloon- and self-expanding transcatheter valve systems, supporting the applicability of this diagnostic tool after 3 months. [27] SPECT is an attractive alternative, as it is thought to be more specific in PVE, but has not been studied in the TAVI population. [19]

In our analysis, nuclear imaging, predominantly ^{18}F -FDG PET, was only used in 25% of patients with negative echocardiography indicating that this diagnostic approach is still not implemented

in daily clinical routine or has not been considered in those high-risk patients. Nuclear imaging was able to confirm radiolabeled tracer localization in 50% of IE-neg. Comparable to PVE, nuclear imaging has the potential to improve the sensitivity of the modified Duke criteria in TAVI-IE.

Impact of negative echocardiography on clinical outcome. IE-neg compared with IE-pos had the same dismal prognosis for in-hospital and 1-year all-cause mortality. Several reasons might have contributed to that finding. First, diagnosis is frequently delayed in cases with negative imaging, potentially leading to deferred treatment initiation. Second, we observed a higher rate of *staphylococcus aureus* in IE-neg compared with IE-pos. TAVI-IE caused by *staphylococcus aureus* is linked to a higher mortality compared with non-*staphylococcus aureus* TAVI-IE. [28] Third, factors associated with mortality, e.g. septic shock, acute renal failure, stroke or heart failure, were found in IE-neg to be as high as in IE-pos.

Limitations

Several limitations should be accounted for while interpreting these results. First, this international, multicenter registry is voluntary, observational, and non-randomized in nature, with the limitations and potential bias on data collection and analysis inherent to this design. Second, there was no external monitoring to verify the accuracy of data reported by each center. Third, data on multimodality imaging were only available in half of the patients with no information hampering the validity of the results. Data on MSCT were not captured at all in the registry. Fourth, we cannot completely rule out that patients with “isolated” bacteremia are within IE-neg although the combination of 1 major and 3 minor or 1 major and 2 minor Duke criteria was high indicating definite IE.

CONCLUSION

Even with negative echocardiographic imaging, patients who have undergone TAVI and presenting with positive blood cultures are a high-risk patient group with a high suspicion of IE and the need for an early treatment initiation. The role of multimodality imaging needs further investigation in TAVI-IE.

NOTES

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Table 1. Baseline characteristics, comparison between patients with and without vegetation

	IE-neg (n=87)	IE-pos (n=491)	Unadjusted p-value ^a	Unadjusted OR (95% CI) ^b
Baseline characteristics				
Gender, male, n (%)	49 (56.3)	312 (63.5)	0.200	0.74 (0.47-1.17)
Age, years mean \pm SD	79.5 \pm 6.3	78.6 \pm 7.7	0.220	1.02 (0.99-1.05)
Body mass index (kg/m ²) mean \pm SD	28.1 \pm 6.0	27.9 \pm 5.8	0.799	1.00 (0.96-1.04)

Diabetes mellitus, n (%)	38 (43.7)	178 (36.3)	0.187	1.36 (0.86-2.16)
COPD, n (%)	22 (25.3)	136 (27.7)	0.642	0.88 (0.52-1.49)
Atrial fibrillation, n (%)	38 (43.7)	209 (42.7)	0.859	1.04 (0.66-1.65)
Chronic kidney disease, n (%)	36 (42.4)	212 (43.7)	0.816	0.95 (0.59-1.51)
Previous Stroke, n (%)	11 (12.6)	64 (13.0)	0.920	0.97 (0.49-1.92)
Previous heart surgery, n (%)	21 (24.1)	108 (22.0)	0.658	1.13 (0.66-1.93)
Previous infective endocarditis, n (%)	1 (1.2)	5 (1.0)	0.999	1.13 (0.13-9.75)
Logistic EuroSCORE, % median (IQR)	15.0 (10.1-25.2)	13.8 (8.0-22.5)	0.056	1.01 (1.00-1.03)
Left ventricular ejection fraction, % median (IQR)	58 (44-65)	57 (47-60)	0.507	1.00 (0.99-1.02)
Mitral regurgitation ≥ 2 , n (%)	12 (13.8)	130 (26.5)	0.010	0.42 (0.22-0.80)
Mean transaortic gradient, median (IQR), mmHg	43 (33.5-52)	44 (34.7-55)	0.249	0.99 (0.98-1.01)
Periprocedural characteristics				
Implantation site				
Catheterization laboratory, n (%)	30 (34.5)	203 (41.3)	0.229	1.34 (0.83-2.16) ^c
Operating and hybrid room, n (%)	57 (65.5)	288 (58.7)		
Approach, n (%)				
Transfemoral	83 (95.4)	424 (86.7)	0.021	3.18 (1.13-8.97)
Prosthesis type				
Balloon-expandable, n (%)	33 (37.9)	265 (55.0)	0.003	0.50 (0.31-0.80) ^d
Self-expanding, n (%)	54 (62.1)	217 (45.0)		
Antibiotic prophylaxis				
Beta-Lactam alone, n (%)	79 (98.8)	399 (93.0)	0.134	5.94 (0.80-44.2) ^e
Vancomycine alone or in combination, n (%)	1 (1.3)	19 (4.4)		
Other	0 (0)	11 (2.6)		
In-hospital Outcomes (TAVI)				
Acute renal failure, n (%)	15 (17.4)	59 (12.3)	0.195	1.50 (0.81-2.80)
Stroke, n (%)	8 (9.3)	19 (4.0)	0.033	2.48 (1.05-5.87)
Major vascular complication, n (%)	10 (11.6)	28 (5.6)	0.049	2.12 (0.99-4.54)
Major bleeding, n (%)	12 (14.0)	41 (8.6)	0.114	1.73 (0.87-3.45)
Sepsis, n (%)	10 (15.4)	45 (9.9)	0.176	1.66 (0.79-3.48)
New pacemaker implantation, n (%)	21 (24.1)	84 (17.2)	0.121	1.53 (0.89-2.64)

Residual aortic regurgitation ≥ 2 at discharge, n (%)	12 (14.6)	69 (14.4)	0.951	1.02 (0.53-1.98)
Mean residual transaortic gradient, median (IQR), mm Hg	10 (8-12)	10 (7-14)	0.786	1.00 (0.96-1.04)
Length of hospital stay, median (IQR), days	11 [7-18]	8.5[6-14]	0.008	1.01 (1.00-1.02)

Values are n (%), median (IQR) or mean (SD). IE-neg indicates infective endocarditis without echocardiographic evidence; IE-pos, infective endocarditis with echocardiographic evidence; SD, standard deviation; COPD, chronic obstructive lung disease; IQR, interquartile range; TAVI, transcatheter aortic valve implantation.

^a *P* values are results of comparing IE-neg vs IE-pos.

^b Unadjusted odds ratio (OR) are results of comparing IE-neg vs IE-pos.

^c Operating/hybrid room as reference.

^d Balloon-expandable as reference.

^e Beta-Lactam as reference.

Table 2. Main clinical characteristics, management, and outcomes of IE episode by presence of echocardiographic evidence of IE.

	IE-neg (N=87)	IE-pos (N=491)	Unadjusted <i>p</i> -value ^a	Unadjusted OR/HR (95% CI) ^b
Time from TAVR, median (IQR), days	129 (20-446)	188 (63-463)	0.051	1.00 (1.00-1.00)
Early IE (within 1 year), n (%)	60 (69.0)	327 (66.6)	0.665	1.11 (0.68-1.82)
Late IE (> 1 year), n (%)	27 (31.0)	164 (33.4)		
Very early (within one month), n (%)	26 (29.9)	65 (13.2)	<0.001	2.79 (1.65-4.74)
Initial symptoms				
Fever, n (%)	69 (81.2)	374 (78.1)	0.521	1.21 (0.67-2.17)
New-onset heart failure, n (%)	31 (36.5)	206 (43.2)	0.248	0.76 (0.47-1.22)
Neurological, n (%)	19 (22.1)	86 (18.1)	0.383	1.28 (0.73-2.25)
Systemic embolism, n (%)	9 (10.5)	64 (13.5)	0.445	0.75 (0.36-1.57)
Skin lesions, n (%)	6 (7.0)	18 (3.8)	0.180	1.9 (0.73-4.93)
Health care-associated infection, n (%)	34 (39.1)	216 (44.0)	0.394	0.82 (0.51-1.30)
Echocardiographic findings, No./total (%)				
Perivalvular extension	0 (0)	105 (21.4)	<0.001	N/A
Valve involved				
Mitral valve	0 (0)	86 (17.5)	<0.001	N/A
Isolated THV	0 (0)	284 (57.8)	<0.001	N/A
Right sided	0 (0)	32 (6.5)	0.009	N/A
Multiple localizations	0 (0)	89 (18.1)	<0.001	N/A

Mean Gradient, mmHg. median (IQR)	10.5 (8-15)	12 (8-18.7)	0.086	0.97 (0.94-1.01)
Increase mean gradient \geq 5mmHg, n (%)	8 (9.2)	88 (17.9)	0.044	0.46 (0.22-0.99)
Increase mean gradient \geq 10mmHg, n (%)	3 (3.5)	48 (9.8)	0.055	0.33 (0.10-1.08)
New aortic regurgitation, n (%)	8 (9.2)	51 (10.4)	0.735	0.87 (0.40-1.91)
New mitral regurgitation, n (%)	4 (4.6)	64 (13.0)	0.024	0.32 (0.11-0.91)
Causative microorganisms, No./total (%)				
<i>Staphylococcus aureus</i> , n (%)	29/86 (33.7)	108/466 (23.2)	0.038	1.68 (1.03-2.77)
<i>Methicillin-resistant</i>	3/29 (10.3)	22/108 (20.4)	0.215	0.76 (0.22-2.60)
Coagulase-negative staphylococci, n (%)	4/86 (4.7)	93/466 (20.0)	0.001	0.20 (0.07-0.55)
<i>Methicillin-resistant</i>	2/4 (50)	26/93 (28.0)	0.341	0.42 (0.10-1.81)
Enterococci, n (%)	32/86 (37.2)	111/466 (23.8)	0.009	1.90 (1.17-3.08)
Streptococci				
<i>S. viridans</i> , n (%)	10/86 (11.6)	61/466 (13.1)	0.710	0.87 (0.43-1.78)
<i>S. gallolyticus</i> (<i>S. bovis</i>), n (%)	5/86 (5.8)	21/466 (4.5)	0.599	1.31 (0.48-3.57)
Others, n (%)	3/86 (3.5)	19/466 (4.1)	0.999	0.99 (0.93-1.06)
Culture negative, n (%)	0 (0)	34 (7.3)	0.010	N/A
Presumed source of entry, n (%)				
Unknown, n (%)	25 (28.7)	180 (37.7)		
Procedural TAVR related, n (%)	3 (3.5)	24 (5.0)		
Urological, n (%)	7 (8.1)	44 (9.2)		
Odontological, n (%)	4 (4.6)	15 (3.1)		
Pacemaker implantation, n (%)	1 (1.2)	11 (2.3)		N/A
Skin/soft tissue infection, n (%)	2 (2.3)	17 (3.6)		
Digestive, n (%)	4 (4.6)	34 (7.1)		
Cancer, n (%)	1 (1.2)	4 (0.8)		
Complications during IE hospitalization No./total (%)				
Any complication, n (%)	55 (63.2)	333 (67.8)	0.400	0.82 (0.51-1.31)
Heart failure, n (%)	31/86 (36.1)	203/464 (43.8)	0.184	0.72 (0.45-1.17)
Acute renal failure, n (%)	34/74 (46.0)	179/438 (40.9)	0.412	1.23 (0.75-2.02)
Septic shock, n (%)	29/85 (34.1)	125/462 (27.1)	0.183	1.40 (0.85-2.29)
Stroke, n (%)	7/86 (8.1)	50/464 (10.8)	0.461	0.73 (0.32-1.68)
Systemic embolization, n (%)	5/85 (5.9)	53/463 (11.5)	0.125	0.48 (0.19-1.25)

Persistent bacteremia, n (%)	14/60 (23.3)	134/424 (31.6)	0.193	0.66 (0.35-1.24)
Management and Outcomes, No./Total (%)				
Antibiotic treatment alone, n (%)	84/87 (96.6)	376/477 (78.8)	<0.001	0.13 (0.04-0.43)
Antibiotic + Surgery during IE hospitalization, n (%)	3/87 (3.5)	101/477 (21.2)		
Time to surgery, median (IQR), days	15.0 [4-135]	17 [6-41]	0.952	1.00 (0.99-1.01)
Transcatheter valve in valve, n (%)	0/29 (0)	3/213 (1.4)	0.520	N/A
Isolated pacemaker extraction, n (%)	0/29 (0)	8/214 (3.7)	0.290	N/A
In-hospital mortality, n (%)	35/87 (40.2)	152/480 (31.7)	0.118	1.45 (0.91-2.32) ^c
Overall mortality, n (%) ^d	55/87(63.2)	288/491 (58.7)	0.425 ^e	1.21 (0.76-1.94) ^c
1-year mortality rate, % (95% CI) ^d	54.2 [43.8-65.4]	48.2 [43.7-53.0]	0.154 ^e	1.26 (0.92-1.74) ^c
Follow-up, median (IQR), months ^f	13.7 [4.6-32.7]	17.2 [6.3-31.0]	0.642	1.00 (0.98-1.01) ^c

Values are n (%) or median (IQR). IE-neg indicates infective endocarditis without echocardiographic evidence; IE-pos, infective endocarditis with echocardiographic evidence; IQR, interquartile range; THV, transcatheter heart valve.

^a P values are results of comparing IE-neg vs IE-pos.

^b Unadjusted odds ratio (OR)/hazard ratios (HR) are results of comparing IE-neg vs IE-pos.

^c Hazard ratio (95%-confidence interval)

^d Kaplan-Meier estimates

^e Log-rank test

^f Patients who survived in-hospital period

Table 3. Factors associated with in-hospital mortality.

	Unadjusted Odds ratios	Unadjusted p-value	Adjusted Odds Ratios	Adjusted p-value
Baseline characteristics				
Chronic kidney disease ^a	1.90 (1.33-2.72)	0.018		
Logistic EuroSCORE ^a	1.02 (1.00-1.03)	0.013		
Left ventricular ejection fraction	0.99 (0.98-1.00)	0.095	0.99 (0.97-1.01)	0.314
Mean aortic gradient	0.99 (0.98-1.00)	0.037	1.00 (0.98-1.02)	0.790
Periprocedural characteristics				
In-hospital Outcomes (TAVI)				
Acute renal failure ^a	2.03 (1.24-3.34)	0.005		
Stroke ^a	2.12 (0.96-4.68)	0.062		
Major bleeding	2.13 (1.20-3.77)	0.009	2.24 (0.76-6.59)	0.142

Sepsis ^a	2.77 (1.57-4.88)	<0.001		
Initial symptoms				
New-onset heart failure ^a	2.35 (1.64-3.38)	<0.001		
Neurological ^a	2.03 (1.32-3.15)	0.001		
Echocardiographic findings				
No echocardiographic finding	1.45 (0.91-2.32)	0.119	1.51 (0.55-4.12)	0.420
Causative microorganismes				
<i>Staphylococcus aureus</i>	2.49 (1.67-3.72)	<0.001	0.96 (0.46-2.02)	0.913
Streptococci	0.39 (0.23-0.65)	<0.001	1.06 (0.48-2.34)	0.886
Complications during IE hospitalization				
Heart failure	4.22 (2.88-6.18)	<0.001	2.36 (1.25-4.46)	0.008
Acute renal failure	4.50 (3.04-6.65)	<0.001	1.81 (0.96-3.40)	0.065
Septic shock	21.00 (13.03-33.85)	<0.001	9.22 (4.77-17.83)	<0.001
Stroke	2.90 (1.66-5.09)	<0.001	4.30 (1.73-10.73)	0.002
Systemic embolism	1.73 (0.99-3.02)	0.054	0.74 (0.31-1.78)	0.497
Persistent bacteremia	8.45 (5.41-13.19)	<0.001	6.71 (3.62-12.44)	<0.001

IE indicates infective endocarditis; TAVI, transcatheter aortic valve implantation.

^a Not included in the multivariable model to avoid collinearity

Table 4. Factors associated with 1-year mortality

	Unadjusted Hazard ratios	Unadjusted <i>p</i>-value	Adjusted Hazard Ratios	Adjusted <i>p</i>-value
Baseline characteristics				
Male gender	0.79 (0.62-1.01)	0.061	0.78 (0.55-1.09)	0.145
Chronic kidney disease ^a	1.71 (1.34-2.19)	<0.001		
Logistic EuroSCORE ^a	1.01 (1.01-1.02)	0.002		
Left ventricular ejection fraction	0.99 (0.98-1.0)	0.056	0.99 (0.98-1.00)	0.091
Mean transaortic gradient	0.99 (0.98-1.00)	0.059	1.00 (0.99-1.01)	0.662
In-hospital Outcomes (TAVR)				

Acute renal failure ^a	1.75 (1.28-2.39)	<0.001		
Stroke ^a	1.58 (0.95-2.61)	0.078		
Major bleeding	1.90 (1.33-2.70)	<0.001	1.67 (1.00-2.79)	0.048
Sepsis ^a	1.68 (1.16-2.43)	0.006		
Initial symptoms				
New-onset heart failure ^a	1.99 (1.55-2.55)	<0.001		
Neurological ^a	1.50 (1.12-2.01)	0.007		
Echocardiographic findings				
Perivalvular extension	1.30 (0.97-1.75)	0.077	1.15 (0.79-1.67)	0.478
No echocardiographic findings	1.26 (0.91-1.74)	0.156	1.10 (0.67-1.80)	0.711
Causative microorganisms				
<i>Staphylococcus aureus</i>	1.90 (1.46-2.47)	<0.001	1.08 (0.74-1.58)	0.686
Streptococci	0.44 (0.30-0.64)	<0.001	1.03 (0.65-1.63)	0.899
Culture negative	1.54 (0.96-2.46)	0.071	1.37 (0.78-2.43)	0.276
Complications during IE hospitalization				
Heart failure	2.85 (2.21-3.69)	<0.001	1.73 (1.19-2.52)	0.004
Acute renal failure	3.11 (2.39-4.04)	<0.001	1.88 (1.30-2.72)	0.001
Septic shock	6.15 (4.75-7.96)	<0.001	2.65 (1.83-3.84)	<0.001
Stroke	1.78 (1.24-2.55)	0.002	1.19 (0.77-1.85)	0.439
Systemic embolization	1.52 (1.05-2.20)	0.025	1.21 (0.80-1.87)	0.400
Persistent bacteremia	3.83 (2.89-5.07)	<0.001	2.01 (1.42-2.84)	<0.001

IE indicates infective endocarditis; TAVI, transcatheter aortic valve implantation.

^a Not included in the multivariable model to avoid collinearity

Table 5. Multimodality imaging in patient with and without echocardiographic evidence of IE

	IE-neg	IE-pos	p-value^a
¹⁸ F-FDG PET	9/40 (22.5)	32/220 (14.6)	0.204
Leucocyte scintigraphy (WBC SPECT/CT)	1/40 (2.5)	2/220 (0.9)	0.386
Radiolabeled tracer localization			

	None	Valve	Periannular	Multiple localization	Other
IE-neg	5/10 (50)	2/10 (20)	2/10 (20)	1/10 (10)	0 (0)
IE-pos	6/34 (17.6)	9/34 (26.5)	16/34 (47.1)	1/34 (2.9)	2/34 (5.9)

Values are n (%). IE-neg indicates infective endocarditis without echocardiographic evidence; IE-pos, infective endocarditis with echocardiographic evidence, ^{18}F -FDG PET, ^{18}F -fluorodeoxyglucose positron emission tomography; WBC SPECT/CT, white blood cell single-photon emission computed tomography/computed tomography

^a *P* values are results of comparing IE-neg vs IE-pos.

FIGURE LEGEND

Figure 1 – Unadjusted all-cause mortality according to absent echocardiographic signs (IE-neg) and evident echocardiographic signs (IE-pos) of infective endocarditis.

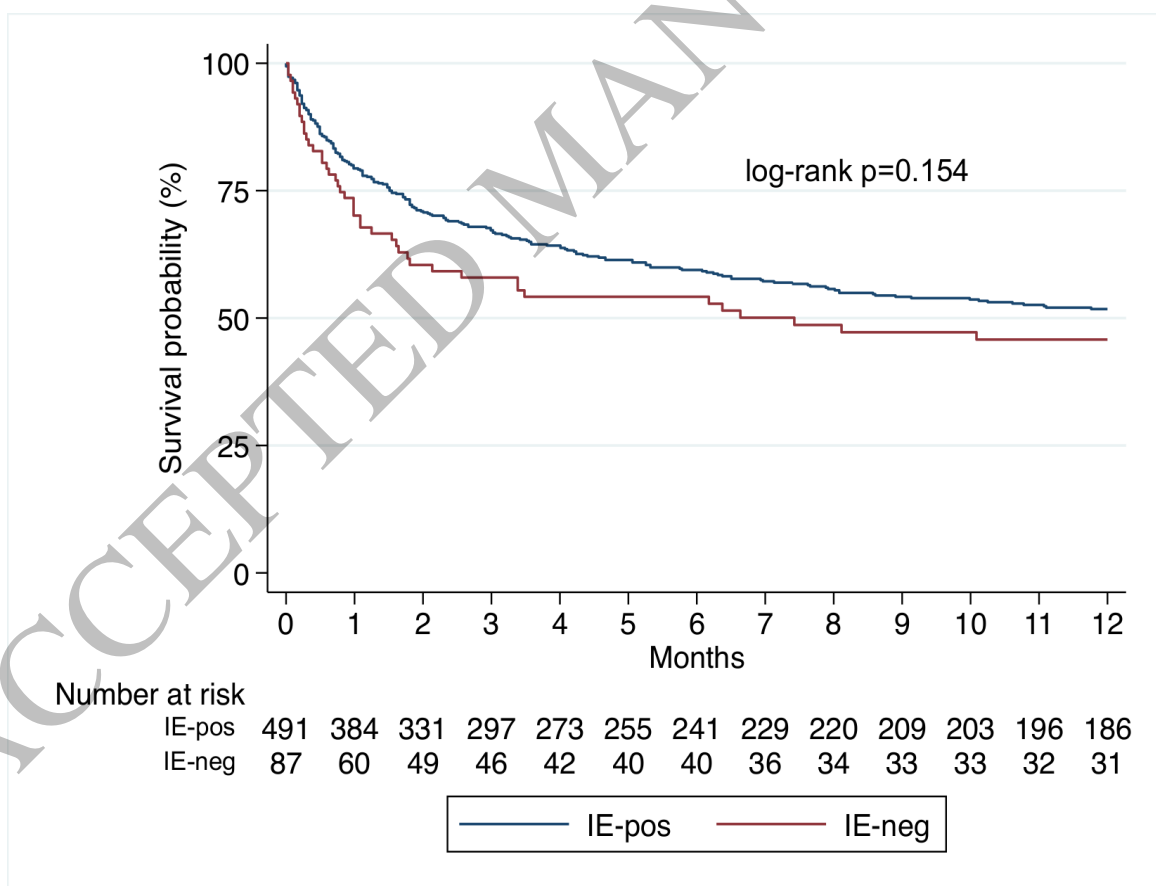
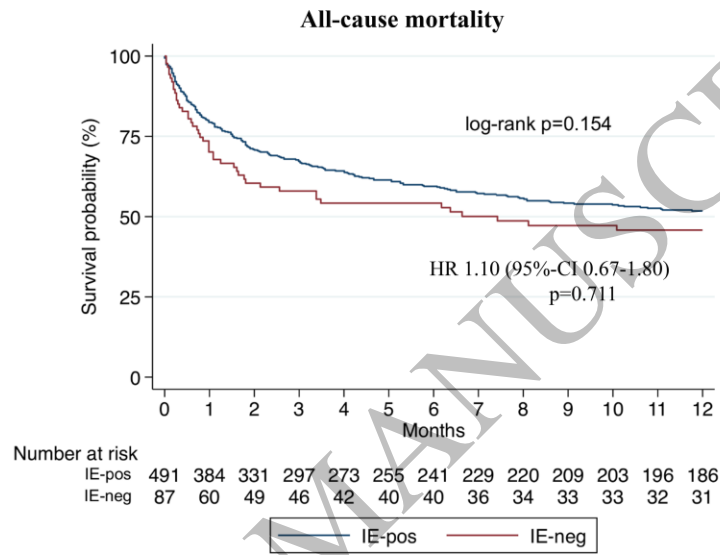


Figure 1
140x102 mm (.23 x DPI)

Impact Of Absent Echocardiographic Signs In Patients With Infective Endocarditis After Transcatheter Aortic Valve Implantation

Infective endocarditis without typical echocardiographic findings (IE-neg) n=87/578 (15%) vs. Infective endocarditis with typical echocardiographic findings (IE-pos) n=491/578 (85%)



Graphical abstract