Structural Heart 6 (2022) 100005

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Original Research

# Transcatheter Aortic Valve Replacement–Associated Infective Endocarditis: Comparison of Early, Intermediate, and Late-Onset Cases

Simrat Kaur, MD [a], Gursharan Singh Samra, MD [a], Manpreet Kaur, MD [b], Nabin K. Shrestha, MD [c], Steven Gordon, MD [c], E. Murat Tuzcu, MD [d], Samir Kapadia, MD [e], Amar Krishnaswamy, MD [e], Grant W. Reed, MD, MSc [e], Rishi Puri, MD, PhD [e], Lars G. Svensson, MD, PhD [f], Wael A. Jaber, MD [b], Brian P. Griffin, MD [b], Bo Xu, MD [b,*]

[a] *Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, USA*
[b] *Section of Cardiovascular Imaging, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Sydell and Arnold Miller Family Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA*
[c] *Department of Infectious Diseases, Cleveland Clinic, Cleveland, Ohio, USA*
[d] *Heart and Vascular Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE*
[e] *Section of Cardiovascular Intervention, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Sydell and Arnold Miller Family Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA*
[f] *Sydell and Arnold Miller Family Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA*

ARTICLE INFO

*Article history:*
Submitted 9 September 2021
Revised 30 November 2021
Accepted 30 December 2021
Available online 17 March 2022

*Keywords:*
Echocardiography
Infective endocarditis
PET/CT imaging
TAVR

ABSTRACT

*Background:* Transcatheter aortic valve replacement–associated infective endocarditis (TAVR-IE) is a relatively rare complication of TAVR. Little is known about the characteristics of early, intermediate, and late-onset TAVR-IE.

*Methods:* We studied the risk factors, microbiological patterns, and diagnostic and treatment strategies in patients with early (<60 days), intermediate (60-365 days), and late-onset (>1 year) TAVR-IE.

*Results:* Ten out of 494 definite cases of prosthetic valve IE between 2007 and 2019 were confirmed to have TAVR-IE from the IE registry at our center. The mean age was 78.1 ± 13.7 years, with 50% being female. The mean Society of Thoracic Surgeons risk score was 7.8 ± 5.7. Most (60%) TAVR-IE cases had an intermediate onset, with *Staphylococcus aureus* being the most common organism (66.6%). 18-fluorodeoxyglucose positron emission tomography aided in diagnosis of TAVR-IE in 20% of cases. Mortality due to IE was observed in 40% of cases. Most of the patients underwent conservative management, and 37.5% survived over a mean follow-up of 709 ± 453 days. Two patients underwent surgery, of whom one died on day 30 postoperatively from sepsis. Mortality due to IE occurred in 25% of cases in the early and intermediate-onset groups, while there was 100% mortality in the late-onset group.

*Conclusions:* In a single-center cohort, most TAVR-IE cases had an intermediate onset, with *Staphylococcus aureus* being the most common organism. Understanding timing of TAVR-IE may have important prognostic implications.

ABBREVIATIONS

18-FDG-PET, 18-fluorodeoxyglucose positron emission tomography; ICD, implantable cardioverter defibrillator; IE, infective endocarditis; SAVR, surgical aortic valve replacement; SAVR-IE, surgical aortic valve replacement associated infective endocarditis; TAVR, transcatheter aortic valve replacement; TAVR-IE, transcatheter aortic valve replacement associated infective endocarditis.

* Address correspondence to: Bo Xu, MD, FRACP, FACC, FASE, Section of Cardiovascular Imaging, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, Sydell and Arnold Miller Family Heart, Vascular and Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, Desk J1-5, Cleveland, OH 44195
*E-mail address:* xub@ccf.org (B. Xu).

https://doi.org/10.1016/j.shj.2022.100005

**Table 1**
Characteristics of the study cohort

| Onset of TAVR-IE | Diagnosis after TAVR implant (d) | Age, gender | BMI | Type of TAVR prosthesis | Pathogen | Imaging tests | Imaging characteristics | Intervention | Timing of mortality | Cause of mortality |
|---|---|---|---|---|---|---|---|---|---|---|
| Early (<60 d) | 58 | 64, M | 63 | 26 mm ES XT | MSSA | TTE/TEE Positive findings on TEE | Multiple mobile vegetations on of the prosthetic leaflets. Largest: 2.7 × 1.1 cm. | - | 15 d | Severe sepsis |
| | 59 | 70, F | 31 | 29 mm Core Valve | *Pseudomonas aeruginosa* | TTE/TEE/noncontrast CT | Posterior paravalular leak. No vegetations on echo or CT. | SAVR with TAVR explantation | - | - |
| Intermediate (61-365 d) | 341 | 83, F | 26 | 26 mm ES | *Enterococcus faecalis* | TTE/TEE Positive findings on TTE and TEE | Mobile echodensity on the ventricular side of prosthetic aortic valve | - | 60 d | Noncardiac |
| | 131 | 93, M | 24 | 26 mm ES | MRSA | TTE/TEE Positive findings on TEE | Large mobile echodensity prolapsing into the aortic root | - | 5 mo | Recurrent infection, septic joint, severe sepsis |
| | 159 | 93, M | 32 | 29 mm ES3 | MSSA | TTE/TEE Positive findings on TEE | Freely mobile prosthetic valvular echodensity prolapsing into LVOT | - | - | - |
| | 280 | 88, M | 23 | 29 mm ES3 | MRSA | TTE/TEE, FDG-PET Positive findings on TTE and TEE | 1.2 × 0.5 cm vegetation on the prosthetic valve strut, FDG uptake on the left coronary prosthetic leaflet | - | 6 mo | Noncardiac |
| | 365 | 58, F | 33 | 29 mm ES XT | MSSA | TTE/TEE Positive findings on TEE | 0.44 cm mobile, filamentous vegetation adjacent to the right coronary prosthetic leaflet | - | - | - |
| | 194 | 80, M | 41 | 29 mm ES XT | MSSE | TTE/TEE, FDG PET Positive findings on TEE | 1.6 × 0.4 cm vegetation on the ventricular side of the prosthetic valve. FDG uptake on the prosthetic aortic valve + ICD lead involvement | ICD removal | - | - |
| Late (>365 d) | 495 | 89, F | 22 | 23 mm ES XT | MRSE | TTE/TEE Positive findings on TEE | 1.1 × 0.4 cm vegetation on the prosthetic aortic valve | - | 4 mo | Recurrent infection, septic emboli to limbs, severe sepsis |
| | 693 | 63, F | 35 | 26 mm ES | *Streptococcus salivarius* | TTE/TEE Positive findings on TTE and TEE | 1.0 x 0.4 cm echodensity on the ventricular side of the prosthetic aortic valve | SAVR, MVR, tricuspid valve repair | 30 d | Severe sepsis, intracerebral hemorrhage |

BMI = body mass index, CT = computed tomography, ES = Edwards Sapien, F = female, ICD = implantable cardioverter defibrillator, LAA = left atrial appendage, M = male, MRSA = methicillin-resistant *Staphylococcus aureus*, MRSE = methicillin-resistant *Staphylococcus epidermidis*, MSSA = methicillin-sensitive *Staphylococcus aureus*, MSSE = methicillin-sensitive *Staphylococcus epidermidis*, MVR = mitral valve replacement, SAVR = surgical aortic valve replacement, TEE = transesophageal echocardiography, TTE = transthoracic echocardiography.

## Introduction

Transcatheter aortic valve replacement (TAVR) has transformed the management of aortic stenosis and is now a preferred procedure in elderly patients with intermediate, high, or prohibitive surgical risk with suitable valve anatomy.[1] TAVR-associated infective endocarditis (TAV-R-IE) is a rare complication of TAVR, associated with high morbidity and mortality.[2] TAVR-IE is not well defined in the literature with data derived mainly from single-center observational experiences or pooled analysis from trials and registries.[3–5] A recent study reported similar temporal incidence and risk of IE between TAVR (5.21 cases per 1000 person-years) and surgical aortic valve replacement (SAVR) (4.10 cases per 1000 person-years; $p = 0.44$), occurring mainly between 31 days and 1 year.[3] Prosthetic valve endocarditis either due to TAVR-IE or SAVR–IE was associated with more than 4-fold increased risk of death in this large cohort study.[3] We aimed to study the characteristics of TAVR-IE with regard to the timing of onset, categorized into early, intermediate, or late onset after implantation.

## Methods

We studied the risk factors, microbiological patterns, and diagnostic and treatment strategies of patients with early (<60 days after TAVR implantation), intermediate (60-365 days after TAVR implantation), and late-onset (>1 year after TAVR implantation) TAVR-IE. Modified Duke's criteria were used to identify cases with definitive TAVR-IE. Clinical, imaging, procedural, and management features were collected using electronic medical records. Definite cases of TAVR-IE were retrospectively identified between 2007 and 2019 from the IE registry at our center after exhaustive retrospective review. This study was approved by the institutional review board (IRB 19-911).

Data points that were collected included age, gender, body mass index, diabetes mellitus, smoking, cancer, hypertension, end-stage renal disease, peripheral vascular disease, stroke or transient ischemic attack, prior cardiac surgery and type, prior episodes of infective endocarditis, microbiological data, Society of Thoracic Surgeons score, and presence of intracardiac devices. The procedural and imaging features included access site, use of preprocedural antibiotics, imaging tests, vegetation size, and spread of infection (intracardiac or extracardiac). The primary endpoint was all-cause death. Continuous variables were expressed as mean (standard deviation), and categorical variables were expressed as frequency and percentages.

## Results

Ten out of 494 definite cases of prosthetic valve IE (10 TAVR valves and 484 surgical valves) between 2007 and 2019 were confirmed to have TAVR-IE from the IE registry at our center. All but 2 cases of TAVR were performed at our center. All cases performed at our center were given preprocedural antibiotics, with cefuroxime being given in 6 cases and vancomycin being administered for 2 patients. The mean age was 78.1 ± 13.7 years, with 50% female. Most (90%) TAVR procedures were performed via a transfemoral route; one had undergone transapical TAVR. Baseline comorbidities were common, with a mean body mass index of 33.1 ± 4.8 kg/m$^2$, diabetes mellitus and hypertension in 60% of cases, and chronic kidney disease in 50% of cases. Four patients had a past medical history of cancer which included endometrial, uterine, breast, and prostate cancer; none of these patients were being actively treated for cancer. The mean Society of Thoracic Surgeons risk score for patients who developed TAVR-IE was 7.8 ± 5.7.

Most (60%) TAVR-IE cases had an intermediate onset, with *Staphylococcus aureus* being the most common organism (66.6%). Diagnostic modalities and complications are described in Table 1. Two cases had early-onset TAVR-IE, one of which was due to *Pseudomonas aeruginosa*, and underwent successful surgical treatment. Late-onset TAVR-IE was observed in 20% of cases, and both patients received intraoperative and postprocedural antibiotics. 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) aided in the diagnosis of TAVR-IE only in 20% of cases, both of which had an intermediate onset, secondary to methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis*, respectively. Echocardiographic studies, including transthoracic and transesophageal echocardiography where appropriate, were utilized in all the confirmed cases. Figure 1 depicts the role of transesophageal echocardiography imaging in TAVR-IE. Mortality due to IE was observed in

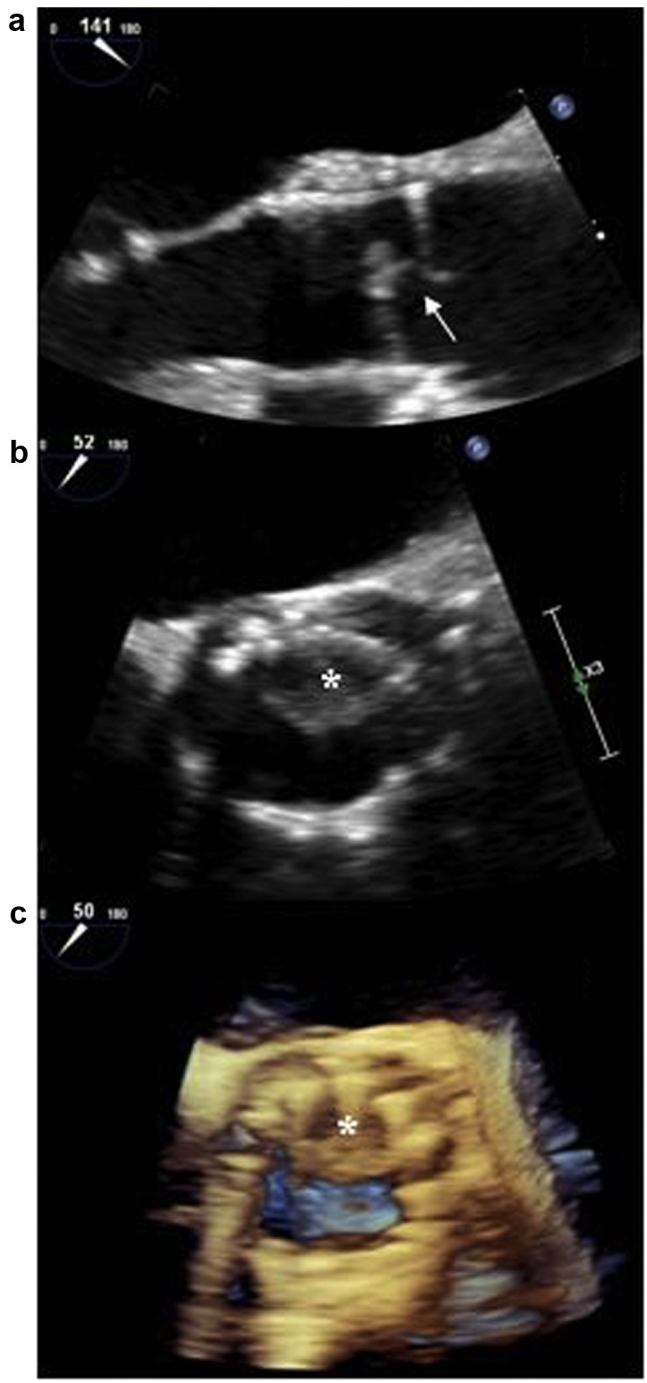


**Figure 1.** Transesophageal echocardiography mid-esophageal long-axis view (a), demonstrating a prominent vegetation attached to the prosthetic leaflets (arrow); Transesophageal echocardiography mid-esophageal short-axis view (b), demonstrating a prominent vegetation arising from the prosthesis posteriorly (*); 3-dimensional transesophageal echocardiography (c) provides further characterization of the prominent vegetation (*).

40% of cases. Most of the patients received conservative management, and 37.5% survived over a mean follow-up of 709 ± 453 days. Two patients underwent surgery, of whom one died 30 days post-operatively from sepsis. Mortality due to IE occurred in 50% of cases in the early-onset (n = 1 of 2) and intermediate-onset (n = 3 of 6) groups, while there was 100% mortality in the late-onset group (n = 2 of 2). No cases of relapsing endocarditis were identified.

## Discussion

This study provides insight into characteristics of TAVR-IE with respect to the timing of onset after TAVR implantation. In this single-center cohort over 13 years, most TAVR-IE cases had an intermediate onset, in agreement with published literature.[3] Published literature reported high rates of infections due to *Staphylococcus*, *Streptococcus*, and *Enterococcus* species.[3,6] In our cohort, *Staphylococcus aureus* was the most common organism identified. This calls for implementation of prophylactic antibiotics utilizing the institutional antibiogram data, which may vary across centers. To minimize potential bacteremia, judicious use of urinary catheters is also important, with early removal to prevent urogenital translocation of *Enterococcus* species. Additionally, patients evaluated for TAVR undergo clinically indicated dental evaluation, with appropriate dental procedures being carried out for select patients.

Our study documents a multimodality imaging approach, including transthoracic and transesophageal echocardiography, and 18-FDG-PET for accurate diagnosis of TAVR-IE.[7] 18-FDG-PET has high false positive rates in the immediate post-TAVR period (<3 months) and should generally only be used in patients without overt imaging evidence of IE on echocardiography and those patients not fully meeting Duke's modified criteria for IE.[2]

Surgical interventions were performed in select patients in our cohort. Decision for surgical intervention was tailored to each individual's hemodynamic status, comorbidities, and operative risk, with each case being managed by the multidisciplinary heart valve team.[2,8] Surgical intervention was often preferred, but those patients with prohibitive surgical risk were conservatively managed. This was similar to the 14% rate of surgery for TAVR-IE from the TAVR international registry (37 out of 250 patients received surgery).[9] Mortality in our cohort was up to 62.5% among patients treated conservatively. In a machine learning risk prediction model for inpatient mortality related to TAVR-IE using the Nationwide Readmission Database, among a total of unweighted 499 hospitalizations of IE after TAVR, the in-hospital mortality was 12%.[10] As highlighted in a recent study based on the Medicare database, 1-year mortality in patients with TAVR-IE was very high at 45.6% (851 out of 1866 patients).[4] This signals an overall poor prognosis of TAVR-IE, highlighting the importance of management of these complex patients in centers with a dedicated, experienced multidisciplinary heart valve team.[11] Our study has some important limitations. Generalizability of the results is limited by the retrospective design and relatively small sample size of our study. TAVR-IE diagnosis is based on clinical, microbiological, and imaging characteristics, and the single-center nature of this study from a quaternary care center potentially captured patients with more subtle findings of endocarditis.

## Conclusion

Understanding the timing of onset of TAVR-IE is prognostically important, because it is potentially associated with differences in microbiological profiles and management outcomes in this contemporary single-center, descriptive cohort study.

## CRediT authorship contributions

All authors meet the criteria for authorship including conception of project or analysis, interpretation of data, drafting of manuscript or revising it critically for important intellectual content, and final approval of the manuscript.

## ORCIDs

Amar Krishnaswamy https://orcid.org/0000-0001-6048-7955
Bo Xu https://orcid.org/0000-0002-2985-7468

## Ethics statement

The research reported has adhered to the relevant ethical guidelines. This retrospective study was approved by the Cleveland Clinic Institutional Review Board (IRB 19-911).

## Funding

The authors have no funding to report.

## Disclosure statement

The authors report no conflict of interest. This work represents original research of all authors and is not published elsewhere. The abstract of this work was presented at the 2020 Scientific Sessions of American Heart Associations.

## References

1 Siontis GCM, Overtchouk P, Cahill TJ, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. *Eur Heart J*. 2019;40(38):3143–3153. https://doi.org/10.1093/eurheartj/ehz275
2 Kaur S, Misbah Rameez R, Jaber W, Griffin BP, Xu B. Transcatheter aortic valve replacement associated infective endocarditis: a clinical update. *Struct Heart*. 2020. https://doi.org/10.1080/24748706.2020.1733718
3 Summers MR, Leon MB, Smith CR, et al. Prosthetic valve endocarditis after TAVR and SAVR: insights from the PARTNER trials. *Circulation*. 2019;140(24):1984–1994. https://doi.org/10.1161/CIRCULATIONAHA.119.041399
4 Mentias A, Girotra S, Desai MY, et al. Incidence, predictors, and outcomes of endocarditis after transcatheter aortic valve replacement in the United States. *JACC Cardiovasc Interv*. 2020;13(17):1973–1982. https://doi.org/10.1016/j.jcin.2020.05.012
5 Brouwer J, van den Brink FS, Nijenhuis VJ, et al. Incidence and outcome of prosthetic valve endocarditis after transcatheter aortic valve replacement in The Netherlands. *Neth Heart J*. 2020;28(10):520–525. https://doi.org/10.1007/s12471-020-01420-2
6 Amat-Santos IJ, Messika-Zeitoun D, Eltchaninoff H, et al. Infective endocarditis after transcatheter aortic valve implantation: results from a large multicenter registry. *Circulation*. 2015;131(18):1566–1574. https://doi.org/10.1161/CIRCULATIONAHA.114.014089
7 Wang TKM, Sánchez-Nadales A, Igbinomwanhia E, Cremer P, Griffin B, Xu B. Diagnosis of infective endocarditis by subtype using (18)F-fluorodeoxyglucose positron emission tomography/computed tomography: a contemporary meta-analysis. *Circ Cardiovasc Imaging*. 2020;13(6):e010600. https://doi.org/10.1161/CIRCIMAGING.120.010600
8 Amat-Santos IJ, Ribeiro HB, Urena M, et al. Prosthetic valve endocarditis after transcatheter valve replacement: a systematic review. *JACC Cardiovasc Interv*. 2015;8(2):334–346. https://doi.org/10.1016/j.jcin.2014.09.013
9 Regueiro A, Linke A, Latib A, et al. Association between transcatheter aortic valve replacement and subsequent infective endocarditis and in-hospital death. *JAMA*. 2016;316(10):1083–1092. https://doi.org/10.1001/jama.2016.12347
10 Bansal A, Mentias A, Jaber W, et al. Machine learning risk model for predicting in-hospital mortality for patients with infective endocarditis after transcatheter aortic valve replacement. *Cardiovasc Revasc Med*. 2021. https://doi.org/10.1016/j.carrev.2021.09.011
11 Agarwal S, Tuzcu EM, Krishnaswamy A, et al. Transcatheter aortic valve replacement: current perspectives and future implications. *Heart*. 2015;101(3):169–177. https://doi.org/10.1136/heartjnl-2014-306254