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FASTTRACK CLINICAL RESEARCH
TAVI

Infective endocarditis after transcatheter aortic valve implantation: a nationwide study

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Aims Transcatheter aortic valve implantation (TAVI), now a common procedure to treat high-risk patients with severe aortic stenosis, has rapidly been expanding into younger and lower-risk populations, creating a need to better understand long-term outcome after TAVI. The aim of the present investigation was to determine the incidence, risk factors for, clinical presentation of, and outcome after prosthetic valve endocarditis (PVE) in patients treated with TAVI in a nationwide study.

Methods and results Three registries were used: a national TAVI registry, a national diagnosis registry, and a national infective endocarditis registry. Combining these registries made it possible to perform a nationwide, all-comers study with independent and validated reporting of PVE in 4336 patients between 2008 and mid-2018. The risk for PVE after TAVI was 1.4% (95% confidence interval 1.0–1.8%) the first year and 0.8% (0.6–1.1%) per year thereafter. One-year survival after PVE diagnosis was 58% (49–68%), and 5-year survival was 29% (17–41%). Body surface area, estimated glomerular filtration rate <30 mL/min/1.73 m^2, critical pre-operative state, mean pre-procedural valve gradient, amount of contrast dye used, transapical access, and atrial fibrillation were identified as independent risk factors for PVE. *Staphylococcus aureus* was more common in early (<1 year) PVE. Infection with *S. aureus*, root abscess, late PVE, and non-community acquisition was associated with higher 6-month mortality.

Conclusion The incidence of PVE was similar to that of surgical bioprostheses. Compromised renal function was a strong risk factor for developing PVE. In the context of PVE, TAVI seems to be a safe option for patients.

Clinical Trial Registration NCT03768180 (http://clinicaltrials.gov/).

Keywords Transcatheter aortic valve implantation • Prosthetic valve endocarditis

Introduction

In the present era, where indications for transcatheter aortic valve implantation (TAVI) are expanding to younger and healthier patients with lower surgical risk, it is imperative to learn more about TAVI's durability and safety over time.[1–6] One feared complication after any valve replacement is prosthetic valve endocarditis (PVE), especially since a valve replacement in itself is a predisposes for PVE.[7,8] A difference in risk for PVE between TAVI and surgical aortic valve replacement (SAVR) would most certainly affect the choice of valve in intermediate- and low-risk patients.

Prosthetic valve endocarditis after a valve replacement or repair is a serious complication associated with high morbidity and mortality. For SAVR, the frequency of PVE has been reported to vary between 0.3% to 1.2% per year, with a higher frequency found in biological valves compared to mechanical valves.[7,9,10] The 10-year cumulative risk for PVE in SAVR patients is about 5%.[11,12] Short-term survival after PVE in SAVR is 75–86%, but 5-year survival is better with reported figures ranging from 65–80%.[9,13] Few reports on PVE after transcatheter valves exist, and the reported incidence during the first year after TAVI varies between 0.1% and 3%.[14–17] The large variation is probably explained by the small numbers in each study, and a two

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subsequent larger multicentre studies found that the risk for PVE the first year was 1.1 and 1.7%, with in-hospital mortality 16% and 36%, and 2-year mortality at 67%.[17,18] However, all these studies are based on selected or small populations with a short follow-up and have limitations in reporting.

The aim of the current investigation was to perform a nationwide, all-comers study of PVE after TAVI with independent and validated reporting up to 10 years after valve implantation.

Methods

Study design

This is a retrospective, nationwide follow-up study of all patients who received a TAVI in Sweden from January 2008 to September 2018, a total of 4336 patients. Data for these patients were extracted from the national TAVI registry SWENTRY (SWEdish traNscatheter cardiac intervention regisTRY), which is a sub-registry of SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) and contains information on all TAVI procedures performed in the country.[19] We excluded patients who received a TAVI in a previously implanted valve ('valve in valve', $n = 206$).

As all Swedish citizens have a unique, lifelong personal identification number mandatory for all governmental and healthcare interactions, complete health histories are guaranteed, and we were able to cross-reference the SWENTRY registry with other registries. The study received approval from the local ethics committee (LU 2017/995) and was registered in www.clinicaltrials.org under the identifier NCT03768180.

Definition of endocarditis

For the diagnosis of PVE, the National Patient Registry ('Patientregistret', NPR) and the Swedish Registry on Infective Endocarditis (SRIE) were used. The NPR contains information on all admissions to hospitals in Sweden, and data entry is mandatory by law. A main discharge diagnosis according to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) is required and the registry allows for multiple secondary diagnoses. To find patients with PVE, we first selected the ICD-10 codes I330, I339, I389, and I398. Patients who had any of the above diagnosis codes as a primary diagnosis or a secondary diagnosis if PVE could be suspected (hospitalization >2 weeks or died before discharge) were included in the first step.

The SRIE registry contains detailed data on 5000 episodes of infective endocarditis (IE) including PVE and is reported by infectious disease specialists in all infectious disease departments around the country.[20] Patients with IE are usually treated in infectious diseases departments, at least during hospitalization. All patients treated for IE are reported to the registry and cases are classified as either possible or definite IE according to the modified Duke criteria.[21] The SRIE lacked complete data on almost half of the patients in the study cohort. Missing cases were retrospectively added by an infectious disease specialist with the help of electronic patient records, creating a complete dataset from the SRIE for the patients in the cohort. Fifteen patients had received an ICD-10 code of IE in the NPR, but were not treated as IE and did not fulfil the modified Duke criteria and were consequently reclassified as not PVE. Two patients were found in the SRIE but not the NPR and were classified as PVE (*Figure 1*). A detailed description of the registries used is provided in the Supplementary material online, *Appendix*. Survival data was extracted from the Swedish Population Registry in January 2019.

Variables in the model

Variables in the SWENTRY registry (Supplementary material online, *Table S1*) were based on the EuroSCORE and VARC-2 definitions.[22,23] The estimated glomerular filtration rate (eGFR) was calculated from creatinine according to the Chronic Kidney Disease Epidemiology Collaboration's formula.[24] Body surface area (BSA) was calculated according to the formula by Du Bois and Du Bois.[25] IE 1-year prior to procedure was constructed from the NPR. Other variables were collected directly or derived from the SWENTRY and SRIE. Valve type was divided into two groups (Supplementary material online, *Table S2*): Self-expandable valve (SEV) or balloon-expandable valve/mechanically expandable valve (BEV/MEV).

Statistical analysis

Kaplan-Meier curves were used to illustrate accumulated PVE incidence and survival after PVE. A Cox proportional hazard model was used to find risk factors associated with PVE during the complete follow-up and the post 1-year analysis. A binary logistic regression was used for determining risk factors for PVE during the first year. Data were complete in all but 41 (two of which were diagnosed with PVE) cases, and these cases were excluded in the multivariable analysis but remained when describing the population. Variables were selected if significant ($P < 0.1$) in univariable Cox analysis or had clinical interest (age, diabetes, peripheral vascular disease, valve type, and new permanent pacemaker). The same selection was made in the analysis for the complete, 1-year, and post 1-year follow-up. A Backwards Stepwise Wald-based exclusion was used with a $P < 0.1$ to stay in the model. After the final model was built, the excluded risk factors were added one by one to see if the model changed significantly. Martingale residuals were used to assess goodness of fit. The proportional hazard assumption in the Cox model was tested using a time-dependent variable. Only the first episode of PVE was analysed. The Student's *t*-test, χ^2 test, or Mann–Whitney *U*-test was performed depending on the distribution of data. Data are presented as mean ± standard deviation (SD), *n* (%), or median with interquartile range (IQR). A *P*-value <0.05 was considered statistically significant. Data analysis was performed using the SPSS package version 25 (IBM Corp., Armonk, NY, USA).

Results

Patients were followed for a median 25.1 (IQR 11.7–43.7) months, yielding a total of 10 555 patient-years for the study. Of the 4336 patients, 103 patients had one episode of PVE, six of these had a second episode of endocarditis, and no patient had a third episode of PVE. The incidence of PVE was 1.42% (1.03–1.80%) for the first year, 0.80% (0.60–1.06%) for 1–5 years, and 0.52% (0.20–1.32%) for 5–10 years (Supplementary material online, *Table S3*, *Figures 2 and Take home figure*). When the material was divided into early (<1 year after implant) and late (>1 year after implant), 51 had an early PVE and 52 had a late PVE (Supplementary material online, *Table S4*).

Risk factors for developing prosthetic valve endocarditis

Univariable Cox analysis detected male gender, larger patients (height, weight, body mass index, and BSA), renal function (s-creatinine, eGFR, and eGFR< 30 mL/min/1.73 m^2), hypertension, critical pre-operative state, atrial fibrillation, history of malignancy, pre-procedural mean aortic gradient, severely depressed left ventricular ejection fraction, transapical access, amount of contrast dye used,

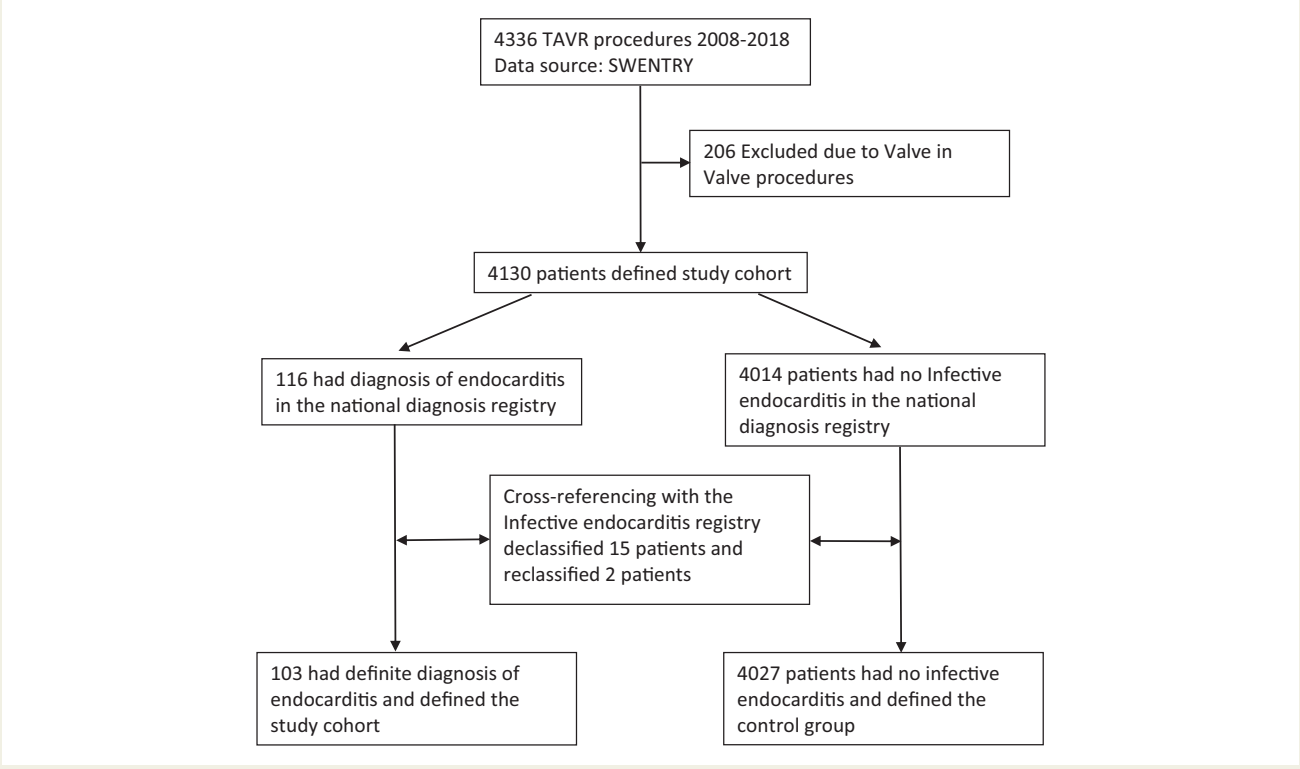


Figure 1 Patient flow. A study flowchart. Nationwide inclusion of patients receiving a transcatheter aortic valve implantation in Sweden since 2008. Group with prosthetic valve endocarditis was defined using the National Patient Registry and the Infective Endocarditis Registry.

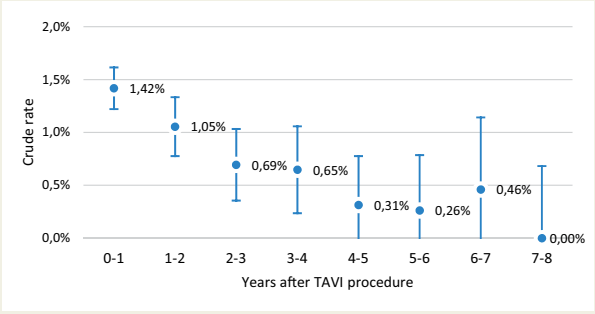
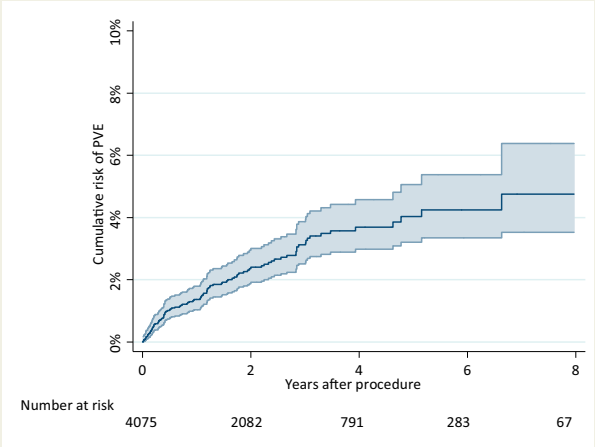


Figure 2 Annual incidence of prosthetic valve endocarditis after transcatheter aortic valve implantation with 95% confidence interval up to 8 years after procedure.



Take home figure Accumulated risk for developing prosthetic valve endocarditis. A Kaplan–Meier failure function for the risk of being diagnosed with prosthetic valve endocarditis in the study population. Curve truncated at 8 years due to small numbers.

prosthesis size, and IE 1 year before TAVI procedure ($P < 0.1$, *Table 1* and Supplementary material online, *Table S1*) as risk factors for developing PVE. In multivariable Cox regression, BSA, eGFR <30 mL/min/1.73 m^2, transapical access, mean aortic gradient, critical pre-operative state, amount of contrast dye used, peripheral vascular disease, and atrial fibrillation remained in the model (*Table 1*). The two most significant risk factors were BSA [HR 1.20 (1.19–1.31) per dm^2, $P < 0.001$] and eGFR < 30 mL/min/1.73 m^2 [HR 2.82 (1.63–4.88), $P < 0.001$, Supplementary material online, *Figure S1*].

Risk factors for early (<1 year) and late (>1 year) PVE were analysed separately. Early PVE was analysed by a binary logistic analysis, and the risk factors were: large BSA, eGFR <30 mL/min/1.73 m^2, high mean aortic gradient, critical pre-operative state, and post-procedural aortic regurgitation Grade I–III (*Table 1*).

Risk factors for late PVE were analysed by a multivariable Cox regression, and large BSA, eGFR <30 mL/min/1.73 m^2, transapical

Table 1 Risk factors for developing PVE

A	Univariable analysis			Multivariable entire follow-up		
Variables	**Wald**	***P*-level**	**HR (95% CI)**	**Wald**	***P*-level**	**HR (95% CI)**
BSA (per dm^2)	15.4	<0.001	1.02 (1.01–1.03)	16.8	<0.001	1.02 (1.01–1.03)
eGFR <30 mL/min/1.73 m^2	13.3	<0.001	2.70 (1.58–4.61)	13.8	<0.001	2.82 (1.63–4.89)
Transapical access	3.3	0.071	2.05 (0.94–4.49)	7.0	0.008	2.14 (1.22–3.77)
Mean gradient (per mmHg)	3.3	0.067	1.01 (1.00–1.02)	6.8	0.009	1.02 (1.00–1.03)
Critical pre-operative state	6.3	0.012	2.89 (1.27–6.59)	4.5	0.033	2.47 (1.08–5.68)
Amount of contrast (per dL)	4.3	0.039	1.28 (1.01–1.63)	5.8	0.016	1.34 (1.06–1.70)
PVD	1.9	0.172	0.68 (0.38–1.19)	4.4	0.036	0.52 (0.28–0.96)
Atrial fibrillation	4.3	0.040	1.50 (1.02–2.22)	3.9	0.047	1.50 (1.01–2.24)
History of malignancy	5.2	0.022	1.82 (1.09–3.03)			
IE in the year before TAVI	2.9	0.090	3.36 (0.83–13.7)			
AR Grade I–III	1.9	0.171	1.31 (0.89–1.94)			
Severely depressed LVEF	2.8	0.092	2.18 (0.88–5.40)			
Diabetes	1.4	0.236	1.30 (0.84–1.99)			
Age (per year)	1.4	0.233	0.98 (0.96–1.01)			
Female gender	5.5	0.019	0.62 (0.42–0.92)			
Hypertension	3.1	0.077	0.69 (0.46–1.04)			
New PPM	0.8	0.363	1.36 (0.70–2.61)			
SEV	1.5	0.214	0.78 (0.53–1.15)			
B	**Logistic regression early PVE**			**Multivariable late PVE**		
Variables	**Wald**	***P*-level**	**OR (95% CI)**	**Wald**	***P*-level**	**HR (95% CI)**
BSA (per dm^2)	14.1	<0.001	1.02 (1.01–1.04)	3.3	0.067	1.01 (1.00–1.02)
eGFR <30 mL/min/1.73 m^2	8.8	0.003	2.95 (1.44–6.03)	4.5	0.033	2.57 (1.08–6.11)
Transapical access				9.8	0.002	3.09 (1.53–6.25)
Mean gradient (per mmHg)	6.9	0.008	1.02 (1.01–1.04)			
Critical pre-operative state	3.2	0.072	2.66 (0.91–7.75)			
Amount of contrast (per dL)				4.8	0.029	1.44 (1.04–2.00)
PVD				3.5	0.062	0.44 (0.18–1.04)
Atrial fibrillation				7.2	0.007	2.16 (1.23–3.78)
History of malignancy				9.4	0.002	2.73 (1.43–5.20)
IE in the year before TAVI				6.4	0.011	6.65 (1.54–28.7)
AR Grade I–III	4.8	0.028	1.91 (1.07–3.41)			

A: Univariable and multivariable Cox analysis of risk factors for developing prosthetic valve endocarditis, sorted in strength in the multivariable analysis. B: Logistic regression for early PVE (1< year) and multivariable Cox analysis for late PVE (1> year).
AR, aortic regurgitation (post-procedural); BSA, body surface area; eGFR, estimated glomerular filtration rate; IE, Infective endocarditis; LVEF, left ventricular ejection fraction; PPM, permanent pacemaker; PVD, peripheral vascular disease; SEV, self-expanding valve; TAVI, transcatheter aortic valve implantation.

access, amount of contrast dye used, peripheral vascular disease, atrial fibrillation, history of malignancy, and IE up to 1 year prior to TAVI procedure remained in the model (*Table 1*).

Clinical presentation

There were 103 patients identified as having PVE, where 54 were classified as definite IE according to the modified Duke criteria (*Table 2*). Alpha-haemolytic streptococci were the most common pathogens, followed by enterococci and *Staphylococcus aureus*. The TAVI valve was deemed to be affected in 50% cases with either vegetation or abscess evident on echocardiography. Echocardiography also found vegetation on the mitral valve in 21% of cases. Open-heart surgery with aortic valve replacement (AVR) was only performed in 2 patients and pacemaker extraction was performed in 11 patients. In-hospital mortality was 16.8% [95% confidence interval (CI) 9.4–24.3%], 1-year survival was 58.2% (95% CI 49.2–68.3%), and 5-year survival was 28.9% (95% CI 16.5–41.2%, *Figure 3*).

A comparison of patients with early (<1 year) and late PVE (>1 year) demonstrated that *S. aureus*, and non-community onset was associated with early IE (*Table 2*).

The risk for death from PVE was defined as death within 6 months from diagnosis and analysed with a binary regression model. In univariable analysis, *S. aureus*, non-community onset, abscess formation, and late-onset of PVE (>1 year) were associated with worse outcome (Supplementary material online, *Table S4*). In the multivariable model, all four risk factors remained significant predictors for

Table 2 Characteristics of patients with prosthetic valve endocarditis, divided as early prosthetic valve endocarditis (<1 year) and late prosthetic valve endocarditis (>1 year)

	All (103)	Early PVE 1< year (*n* = 51)	Late PVE >1> year (*n* = 52)	*P*-value
Age	82 (77–85)	82 (77–85)	83 (78–86)	0.376
Female gender	40 (38.8%)	15 (29.4%)	25 (48.1%)	0.052
Microbiology				
Staphylococcus aureus	23 (22.3%)	16 (31.4%)	7 (13.5%)	0.029
Alpha streptococci	35 (34.0%)	17 (33.3%)	18 (34.6%)	0.891
Enterococcus faecalis	21 (20.4%)	10 (19.6%)	11 (21.2%)	0.846
CoNS	7 (6.8%)	1 (2.0%)	6 (11.5%)	0.053
No bacteria	5 (4.9%)	2 (3.9%)	3 (5.8%)	0.663
Other bacteria	12 (11.7%)	5 (9.8%)	7 (13.5%)	0.563
Definite IE	54 (52.4%)	26 (51.0%)	28 (53.8%)	0.771
Nosocomial	18 (17.8%)	15 (29.4%)	3 (6.0%)	0.002
Community acquisition	76 (74.5%)	33 (64.7%)	43 (84.3%)	0.023
Echocardiography				
TOE performed	83 (81.4%)	41 (80.4%)	42 (82.4%)	0.799
Vegetation on TOE	39 (38.2%)	18 (35.3%)	21 (41.2%)	0.541
Abscess	12 (11.9%)	7 (13.7%)	5 (10.0%)	0.563
New PVL	5 (5.0%)	3 (5.9%)	2 (4.0%)	0.663
Aortic valve affected	54 (52.9%)	26 (51.0%)	28 (54.9%)	0.692
Mitral valve affected	22 (21.8%)	9 (17.6%)	13 (26.0%)	0.309
No vegetation	32 (31.7%)	18 (35.3%)	14 (28.0%)	0.431
PM lead vegetation	6 (6.0%)	2 (3.9%)	4 (8.2%)	0.372
Other				
Vascular phenomena	10 (9.8%)	5 (9.8%)	5 (9.8%)	1
Stroke	8 (7.7%)	6 (11.7%)	2 (3.9%)	0.133
Surgery during hospitalization	13 (12.7%)	6 (11.8%)	7 (13.7%)	0.767
PM extraction	11 (10.8%)	4 (7.8%)	7 (13.7%)	0.338
SAVR during hospitalization	2 (2.0%)	2 (3.9%)	0 (0.0%)	0.161
Hospitalization (days)	38 (25–46)	39 (27–45)	35 (25–47)	0.96
Death during hospitalization	17 (16.8%)	8 (15.7%)	9 (18.0%)	0.756
Death within 6 months of PVE	31 (30.1%)	11 (21.6%)	20 (38.5%)	0.062

CoNS, coagulase negative *Staphylococcus*; PM, pacemaker; SAVR, surgical aortic valve replacement; TOE, transoesophageal echocardiography.

mortality with the following odds ratio: 2.7 (95% CI 0.8–8.9, $P = 0.095$) for *S. aureus*, 4.9 (95% CI 1.1–22.0, $P = 0.037$) for abscess formation, 5.6 (95% CI 1.8–17.5, $P = 0.003$) for late (>1 year) onset, and 5.1 (95% CI 1.6–16.4, $P = 0.006$) for non-community onset.

Discussion

This nationwide, all-comers, registry-based study provides robust information on the incidence, clinical presentation, and outcome of PVE after TAVI in Sweden. We found an increased risk for PVE the first year after TAVI (1.4%) that levelled out the coming 4 years (average 0.8%/year). After PVE diagnosis, the initial prognosis was poor with a 1-year survival of 58%.

This study provides incidence figures for PVE after TAVI up to 10 years, where data for the first 5 years should be considered reliable with the numbers at risk, and our two-step process to identify patients with PVE. Consequently, the question arises how these numbers compare with PVE after SAVR. Glaser *et al.*[10,26] studied the frequency of PVE after SAVR on a national level in Sweden using a similar method to our study, but they did not cross-reference against the National Endocarditis Registry. Still, as the conditions were the same in both studies (patient population, healthcare system, geographic location, definitions, level of intervention, diagnostic tools), their study can act as a comparator. In the first year, Glaser *et al.* found a 0.7% (0.55–0.89%) risk for PVE in mechanical SAVR and a 1.17% (1.01–1.36%) risk for PVE in biological SAVR compared to our findings of a 1.42% (1.03–1.80%) risk for PVE after TAVI. The risk for the first 5 years was 0.43% (0.37–0.51%) for mechanical SAVR and 0.60% (0.53–0.68%) for biological SAVR, as compared to our findings of 0.80% (0.60–1.06%) for TAVI. The risk during years 5–10 after the procedure was 0.38% (0.31–0.46%) for mechanical AVR and 0.59% (0.50–0.70%) for biological SAVR, compared to our study, reporting 0.52% (0.20–1.32%) for TAVI. At all three intervals, there seems to be a numerical trend towards a higher risk of PVE from mechanical to biological SAVR to TAVI. Randomized studies comparing biological

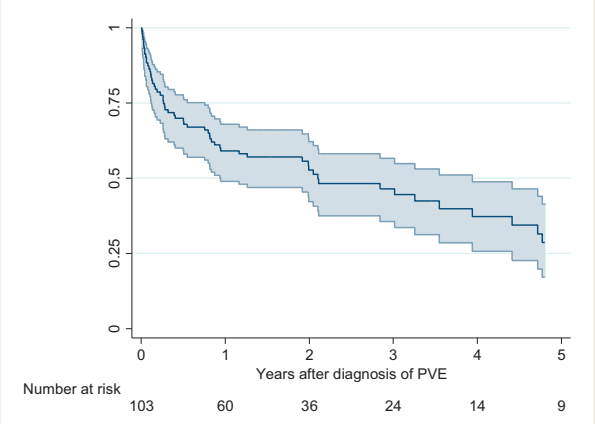


Figure 3 Survival curve after diagnosis of prosthetic valve endocarditis. Kaplan–Meier survival estimates for survival after being diagnosed with prosthetic valve endocarditis, median follow-up 12.8 (interquartile range 3.6–24.0) months.

and mechanical valves have shown conflicting results regarding the risk for PVE.[27–29] Infective endocarditis in native valves increase with age,[30] which could explain the trend observed as older patients have more comorbidities. For instance, we found that renal function was a strong predictor for PVE, and the increasing frequency of renal impairment with age among TAVI patients could be one factor. Prosthetic valve endocarditis rates did not differ in large randomized trials comparing outcome after TAVI and SAVR, where age and renal function are comparable in both groups.[1,31] Therefore, the slightly higher rates of PVE in TAVI is likely explained by comorbidities more than type of valve.

The risk factors identified in the present study are partly at odds with previous reports. In the study by Regueiro *et al.*[17] found that lower age, male sex, diabetes, chronic obstructive pulmonary disease (COPD), residual aortic regurgitation, and orotracheal intubation were associated with PVE. In a study by Mangner *et al.*,[32] lower age, peripheral arterial disease, COPD, renal failure, haemodialysis, postoperative AR grade ≥2 were more common in patients with PVE. In surgical AVR patients, classical risk factors for developing PVE are New York Heart Association (NYHA) functional Class III or IV, alcohol consumption, previous IE, fever during the intensive care unit stay, and gastrointestinal bleeding. Functional class III or IV and complications of the surgical wound were independent predictors of early PVE, whereas postoperative fever and gastrointestinal bleeding were predictors of late PVE.[33] We found BSA and reduced eGFR to be the most significant predictors of PVE. This is mostly new information, as previous studies did not include anthropometric data, and only one study included information on renal function.[32] In the study of Regueiro *et al.*,[17] the correlation between COPD and orotracheal intubation was weak, but a strong correlation was found with residual aortic regurgitation. Our study also found a strong correlation between aortic regurgitation and PVE, but only in early PVE. With the broad selection of potential risk factors in the present study, new risk factors emerged: BSA, amount of contrast dye given, atrial fibrillation, mean pre-procedural gradient, critical pre-operative state, transapical access, and history of malignancy. Many of these are also markers of frailty and reduced mobility (critical pre-operative state, transapical access, and atrial fibrillation), which could explain why they are associated with PVE. Surprisingly, the amount of contrast dye given during the procedure was associated with PVE, but once divided between early and late PVE, it only predicted late PVE. The most likely explanation is that contrast-induced nephropathy, and low pre-procedural renal function are strong predictors for PVE. The strong correlation between BSA and PVE is intriguing. As it was only found in early PVE once analysed separately, it could be speculated that the femoral puncture site could be the port of entry for the bacterium, which is likely more often colonized with *S. aureus* in larger patients.[34] In the univariate analysis, all metrics of patient size were highly significant, and BSA was chosen as it was the strongest (Supplementary material online, *Table S1*). In a *post hoc* analysis, this correlation is mostly driven by the largest quintile (Supplementary material online, *Figure S2*). Mean pre-procedural gradient was also found to be associated with PVE. One feasible explanation is that the more calcified the valve, the more fracturing of the stenotic valve is needed to place the TAVI, creating larger niduses for the bacteria to adhere. Once the endothelial damage has healed, this risk would be eliminated, which is confirmed in our analysis, were mean gradient was not a risk factor for late PVE. Peripheral vascular disease was negatively associated with PVE. This is probably a case of residual confounding explained by a competing risk for death in the analysis. Of interest are also factors that were not associated with PVE. For instance, SEV or BEV/MEV did not differ in risk for PVE. At least one other study have identified orotracheal intubation as a risk factor,[17] and our study did not find such an association. Also, diabetes was not identified, but reduced eGFR and sensitivity to contrast could be a better marker for severity of diabetes as compared to the limited information in the dichotomous variable diabetes.

The most common causative pathogens were alpha streptococci followed by *S. aureus*. The high proportion of alpha streptococci is different from what has been described before possibly as a consequence of our approach to include cases not only from tertiary centres.[17] Not surprisingly, given the high pathogenicity of *S. aureus*, this bacterium was associated with both fatal outcome and early IE whereas alpha streptococci were associated with more favourable outcome. Early infections with pathogens of low pathogenicity such as coagulase-negative staphylococci were rare, indicating that the majority of episodes were caused by haematogenous spread of bacteria to the valves. Only 50% of patients showed signs on transoesophageal echocardiography (TOE) of prosthesis engagement, and at the same time, 21% had engagement of the mitral valve. These figures are similar to what has been reported previously.[17] The lack of TOE findings in a large proportion of cases is probably explained by constraints of the stent frame on ultrasound performance. Alternative modalities such as ECG-gated computed tomography (CT) and positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (FDG-PET/CT) provides additional diagnostic value in cases of PVE, but these procedures were not routinely performed or documented in our cohort.[35]

As this study is retrospective, most of the patients fall in the high or prohibitive risk category. One could, therefore, expect that outcome after PVE to be dismal, and the in-hospital survival was 83%, 1-year survival was only 58%, but the 5-year survival was 29%. The frailty of the patients is also the likely explanation for the very low number of surgical valve replacements performed for treating PVE in our cohort. The survival curve (*Figure 3*) seem to be biphasic, indicating that if patients survive the first year after TAVI, a normal survival curve for this category of patients is reached.

The aim when designing this investigation was to perform a more reliable and robust study by including all TAVI procedures performed in a single country, having independent and structured registration of PVE validated by infectious disease specialists, and following all patients up to the present date. We encountered very few missing data points, eliminating the need for imputation and reducing the risk for attrition bias. Despite these precautions, registries have inherent weaknesses, which are either built into the registry or due to human error when reporting, which can lead to inaccurate or missing data. Still, the two-step independent process for diagnosis is more than retrospective registry studies offer.

Another limitation in clinical practice is that the Duke criteria of a positive echocardiogram finding is hard to meet in TAVI patients, as both the old valve and stent frame obscures the new valve. For this reason, we also included possible IE according to Duke criteria in this study.

From a statistical standpoint, a larger cohort would have yielded more robust statistics, but as all patients who have ever received TAVI in Sweden were included it was impossible to increase the number. To avoid a Type II error in this cohort, we increased the *P*-level to stay in the model to 0.1, which consequently increased the risk for a Type I error. Therefore, results should be interpreted with strength of the correlation in mind.

In this nationwide, all-comers study with virtually complete follow-up, we found that the incidence of PVE after TAVI was only fractionally higher than previously reported for surgical biological prosthesis. Risk factors for developing PVE were poor renal function, high BSA, high pre-operative valve gradient, critical pre-operative state, transapical access, atrial fibrillation, and amount of contrast dye given during procedure. The prognosis after PVE was poor the first 12 months with a 58% survival rate, but the survival rate improved up to 5 years.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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