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Title
Infective endocarditis after surgical and transcatheter aortic valve replacement: a UK nationwide cohort study

Brief Title
Infective endocarditis after SAVR and TAVR: a UK nationwide cohort study

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Summary tweet
Infective endocarditis after #SAVR and #TAVR in the UK: a nationwide cohort study @JACCJournals

Disclosures The authors have nothing to disclose

ABSTRACT

Background: Increasing use of transcatheter aortic valve replacement (TAVR) has led to an expanding population at increased risk of infective endocarditis (IE). The incidence of IE after TAVR over long-term follow-up, compared with surgical aortic valve replacement (SAVR), and the factors that influence risk and outcome are relatively unknown.

Objectives: To define the incidence, risk factors, characteristics and clinical outcomes of IE following TAVR in the United Kingdom (UK), and its relative incidence compared with a large nationwide cohort undergoing SAVR.

Methods: All patients who underwent TAVR or SAVR between 2007- 2016 inclusive were identified from the UK National Institute for Cardiovascular Outcomes Research databases. Hospital admissions with a primary diagnosis of IE were identified by linkage with the NHS Hospital Episode Statistics database. Additional data were obtained from the treating physician.

Results: 157 of 16,014 patients undergoing TAVR developed IE over a median follow-up of 23.8 months - an overall incidence of 3.64 per 1000 person-years. Correspondingly, 2,058 of 91,962 patients undergoing SAVR developed IE over a median follow-up of 53.8 months – an overall incidence of 4.82 per 1000 person-years. The cumulative incidence of IE at 60 months was significantly higher after SAVR than after TAVR (2.4% [95% CI 2.3-2.5] vs. 1.5% [95% CI 1.3-1.8], HR 1.60, $p < 0.001$). IE was significantly more common in men (HR 2.05, 95% CI 1.35-3.11),

in patients receiving mechanically-expandable (HR 2.15, 95% CI 1.16-4.01) and balloon-expandable valves (1.60, 95% CI 1.01-2.52), and in those with an elevated post-procedural peak gradient (HR 1.81, 95% CI 1.23-2.67). Overall survival with TAVR-IE was 54.4% at one year, with adverse outcome associated with shock or stroke.

Conclusions: IE is a rare but important complication of TAVR that carries significant mortality. In our population, the incidence of IE after TAVR seems to be lower than after SAVR.

Key Words

Infective endocarditis; surgical aortic valve replacement; SAVR; transcatheter aortic valve replacement; transcatheter aortic valve implantation; TAVR; TAVI.

Abbreviations

IE – infective endocarditis

CI – confidence interval

HR – hazard ratio

IQR – inter-quartile range

TAVR – transcatheter aortic valve replacement

SAVR – surgical aortic valve replacement

INTRODUCTION

Infective endocarditis (IE) is a life-threatening complication of prosthetic valve replacement which affects approximately 0.3 – 1.0% per person-year, and is challenging to diagnose and treat.[1,2] In the last 15 years, transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of aortic stenosis in patients unfit for surgical valve replacement, or at elevated surgical risk, leading to an expanded population with prosthetic valves. The reported incidence of IE in patients with prosthetic valves is over 100 times that of the general population[3,4] and this risk may be even higher in the elderly group of patients undergoing TAVR who are frequently hospitalized and undergo invasive procedures associated with healthcare-associated bacteraemia.[5]

To date, few studies have systematically evaluated the population risk of IE over long-term follow-up after TAVR. Insights concerning risk factors, clinical characteristics and outcomes have largely been limited to registry studies from tertiary centres with attendant referral bias or incomplete follow-up.[6-9] There is ongoing uncertainty as to which patients with prosthetic valves are most susceptible to IE, and how to reduce this risk.[10] Unlike in Europe and the USA, routine oral antibiotic prophylaxis for at-risk patients undergoing invasive dental procedures has not been recommended in the United Kingdom since 2008.[11,12] Furthermore, the optimal treatment of prosthetic valve IE in patients following TAVR (many of whom have previously been judged unfit for elective valve surgery) is unclear.

In this study, we use nationwide linked registry data to provide insights into the epidemiology of IE following TAVR (TAVR-IE) and surgical aortic valve

replacement (SAVR-IE) in the United Kingdom. We describe the incidence, risk factors, disease characteristics, clinical management and outcome for patients with TAVR-IE, its relative incidence compared with SAVR-IE, and identify risk factors for adverse outcome over long-term follow-up.

METHODS

Design

We performed a retrospective cohort study using database linkage to identify all first episodes of IE in a consecutive series of patients undergoing TAVR or SAVR in the United Kingdom. Ethical approval for the study was provided by the London Bromley Research Ethics Committee (reference 16/LO/0275) and the United Kingdom confidentiality advisory group (reference 17CAG0001).

Study populations

All patients undergoing TAVR or first SAVR (+/- coronary artery bypass grafting) between January 1st 2007 and December 31st 2016 were identified from the United Kingdom TAVR and Adult Cardiac Surgery databases, respectively, held by the National Institute for Cardiovascular Outcomes Research (NICOR). These data are submitted by implanting clinical teams using a web-based interface, with case ascertainment performed by comparing reported centre total procedural numbers with the number of procedures uploaded to NICOR servers.[13] We extracted data concerning baseline patient demographics (age, sex), comorbidities (smoking, atrial fibrillation, previous percutaneous coronary intervention, peripheral vascular disease, kidney disease, pulmonary disease, lung disease, liver disease, prior cardiac surgery), and procedural variables for TAVR alone (access approach, valve type, post-

deployment final transvalvular gradient, and in-hospital complications).

Cases

The National Health Service (NHS) records a primary discharge diagnosis using the ICD-10 coding system in the NHS Digital Hospital Episode Statistics Admitted Patient Care database (HES APC) for all patients admitted to hospital in England. We used linkage between the NICOR datasets and HES APC to identify patients hospitalized with a primary discharge diagnosis of "acute or subacute infectious endocarditis" (ICD-10 I33.0), "endocarditis, valve unspecified" (ICD-10 code I38) or "endocarditis and heart valve disorders in diseases classified elsewhere" (ICD-10 code I39), from any date up to May 1 2017. Only admissions of ≥ 14 days duration were included. To exclude cases of SAVR undertaken for native valve IE, any case with a diagnosis of IE at a timepoint ≤ 3 days from surgery was excluded. NHS Digital performed linkage using a deterministic algorithm to match patients by exact NHS number and at least one other identifier (date of birth and sex). By searching individual patient level data we were able to identify when patients admitted to one hospital were transferred to another, and these continuous periods of illness (so called "superspells") were counted only once. To identify patients with IE following TAVR elsewhere in the United Kingdom (Wales, Scotland and Northern Ireland), contact was made with the three major implanting centres to obtain details of all cases over the study period. For SAVR, cases of IE and total cases are those from England only. Patient-level data regarding clinical presentation, microbiological characteristics, echocardiographic findings, management and complications were then requested from the supervising physician for all cases of TAVR-IE.

Outcomes

The primary outcome was the incidence of IE during follow-up, analyzed as cumulative incidence and incidence rate per person-year.

Statistical analysis

Numerical data are expressed as mean +/- standard deviation or median with interquartile range (IQR). Categorical data are presented as absolute number with percentage. Comparison between groups was performed using the χ^2 or Fisher exact test for categorical variables, and Student's t-test for continuous variables. A p value < 0.05 was defined as significant. All tests were two-sided. Cumulative incidence of IE was calculated in the competing risk setting, using death as a competing risk. Time-to-event data analysis was performed using a Cox proportional hazards model, with Kaplan-Meier survival curves drawn to assess differences between groups for the time to an event. Models were checked for violation of the proportional hazards assumption by assessing log-minus-log survival plots and scaled Schoenfield residuals. For Cox modelling, single variable analysis was used to examine the independent effect of clinical factors on outcome, and only those variables which were significant at $p < 0.1$ were included in the multivariable model. For multivariable models, a backward stepwise model selection approach was used to identify significant risk factors, and independent variables with $p > 0.1$ were sequentially excluded. 95% CIs were calculated. For single variable analyses, patients with missing data for the covariate of interest were excluded. Missing data were assumed to be missing at random, and missing data imputation performed for the multivariable models. Data were analysed with SPSS v 22.0 (IBM Corp., Armonk,

NY, USA) and R (R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

RESULTS

Between January 1st 2007 and December 31st 2016, a total of 16,014 TAVR procedures were performed across the United Kingdom (Figure 1). Patients with a history of IE at any point prior to TAVR (n = 78) were excluded from the analysis, to give a population at risk of first episode of IE. After combining cases from England, Wales and Northern Ireland, a total of 157 cases of IE after TAVR were identified. The median follow-up after TAVR was 23.8 (IQR 7.8-52.4) months, corresponding to an overall incidence of TAVR-IE of 3.6 per 1000 person-years. The cumulative incidence one year following TAVR was 0.7% (95% CI 0.5-0.8).

We then compared the incidence of IE after TAVR with that after SAVR. As expected, the populations undergoing TAVR and SAVR were significantly different (Online Table 1). There were 91,962 SAVR cases undertaken between January 1st 2007 and December 31st 2016, and a total of 2,058 subsequent cases of IE identified over a median follow-up duration of 53.8 months (IQR 22.2-88.6), corresponding to an incidence of 4.82 per 1000 person-years. The cumulative incidence of IE at 60 months was significantly lower after TAVR compared with SAVR (1.5% 95% CI 1.3-1.8 vs. 2.4% 95% CI 2.3-2.5, HR 1.60, $p < 0.001$; Figure 2).

Next, we analysed the demographics of patients with TAVR-IE. Their mean age was 79.2 ± 7.8 years, and 69% were male. The median time to IE following TAVR was

10.0 (IQR 4.0-22.3) months. Of IE cases, 19.8% were admitted within three months of the index TAVR, but 8.28% were admitted more than 36 months following the procedure (Online Figure 1). Baseline clinical characteristics of patients with and without IE following TAVR are shown in Table 1. Patients with IE were younger (p = 0.003) and more commonly male (p = 0.0002). There was no difference in the proportion with a previous history of percutaneous coronary intervention, severe liver disease or dialysis-dependent renal failure, and no relation to overall procedural risk profile (defined by logistic Euroscore). Procedural characteristics of patients with TAVR-IE are shown in Table 2. Most patients in both groups underwent the procedure via transfemoral approach. Use of general anesthesia was more common in patients with IE (p = 0.004), and there was a significant difference in valve design (p = 0.001) and post-deployment peak gradient (p = 0.003).

Cox proportional hazards modelling was performed to identify baseline clinical and procedural factors associated with TAVR-IE (Online Table 2; Table 3). Factors which retained significance on multivariable analysis were male sex (HR 2.05, 95% CI 1.35-3.11, p = 0.001), implantation of a mechanically-expandable or balloon-expandable valve (HR compared with self-expanding valve: 2.15 [95% CI 1.16 – 4.01], p = 0.015 for mechanically-expandable valve; 1.60 [95% CI 1.01-2.52], p = 0.037 for balloon-expandable valve), and post-deployment peak gradient greater than the median of 16mmHg (HR 1.81 [95% CI 1.23-2.67], p = 0.003).

Triggering procedures and disease characteristics of TAVR-IE

Information concerning preceding invasive procedures, clinical presentation and microbiological characteristics were available for 85/157 (54.1%) patients in the

cohort, whose records were reviewed locally by their treating physician. In the 3 months prior to admission with TAVR-IE, a total of 21 patients (24.7%) had undergone an invasive procedure (Table 4). Two patients (2.4%) had undergone dental procedures – in both cases IE was due to oral streptococci. Antibiotic prophylaxis was given at the time of TAVR implantation in all but two centres (32/34, 94%) from whom implant data were available.

Fever was the most frequent clinical feature of TAVR-IE (Online Table 3), recorded in 57 patients (67.1%), followed by symptoms consistent with systemic infection (rigors, sweats) in 25 (29.4%). At admission, 13 patients (15.3%) were in pulmonary oedema. 6 patients (7.1%) presented with a stroke, 2 (2.4%) with an acute coronary syndrome, and 10 patients (11.8%) had evidence of systemic embolism. Non-specific symptoms (including malaise and lethargy) were common and present in 49 patients (57.6%). 58/85 (68.2%) of cases met Duke criteria for a definite diagnosis of IE (Online Table 4).

Blood cultures were positive in 78 patients (91.8%, Table 5). Enterococci were the most common causative organism of TAVR-IE, accounting for 22 (25.9%) of cases, followed by oral streptococci (16.4%), *Staphylococcus aureus* (11.8%) and coagulase negative staphylococci (8.2%).

Findings from transthoracic echocardiography (TTE) were available for 78/157 (49.7%) of cases, and from transesophageal echocardiography (TEE) in 51/157 (32.5%) (Table 6). TEE demonstrated vegetations in 72.5% of patients, most commonly on the TAVR leaflets (58.8%). Paravalvular extension of infection was

identified in 7 (13.7%) of patients with TEE data available and new paravalvular aortic regurgitation in 7 (13.7%).

Management and clinical outcomes of TAVR-IE

Data concerning antibiotic therapy were obtained in 76/154 cases (49.4%) (Online Table 5). Each patient was treated with a median of two antibiotic drugs (range 1-6), with 43 (50.6%) receiving gentamicin.

In-hospital complications of TAVR-IE are shown in Table 6. 32/85 (37.6%) patients had an indication for surgical intervention (defined as pulmonary oedema, cardiogenic shock, periannular abscess or presence of vegetation > 15mm in size on TEE, or persistent bacteraemia despite antibiotic therapy). Of these, only 7 patients (16.7%) underwent surgical intervention (Online Table 6)

Survival to hospital discharge was 61.4%, with survival at one year 54.4% (Figure 3). On single variable analysis (Online Table 7), specific factors associated with one-year mortality were cardiogenic shock (HR 4.6 [95% CI 2.1-10.3], p = 0.0002), septic shock (HR 3.4 [95% CI 1.4-8.3], p = 0.006) and stroke (HR 4.9 [95% CI 1.46-16.7], p = 0.01). These factors retained significance on multivariable analysis (Table 7).

DISCUSSION

The key findings of this study are: (A) in an unselected consecutive nationwide population of over 16,000 patients, the risk of IE following TAVR was 3.64 per 1000 person-years over long-term follow-up, and statistically lower than the incidence after

SAVR (4.82 per 1000 person-years), (B) specific groups were at increased risk, including men, patients with mechanically-expandable or balloon-expandable valves, and those with an elevated post-deployment transvalvular gradient, (C) presentation was commonly non-specific, and fever or malaise in a patient post-TAVR may be the only symptom of IE, (D) enterococci were the most common cause of TAVR-IE, and (E) prognosis was extremely poor, particularly in patients presenting with shock or stroke.

Risk of infective endocarditis following TAVR

Previous studies have reported an incidence of TAVR-IE between 0.3-2.1 per 100 patient years.(7,8,14-21) Kolte *et* al first analysed the relative incidence of IE following TAVR and SAVR, reporting incidences of 1.7 and 2.5 per 100 person-years, respectively, and no statistically significant difference between the two groups.[16] Similarly, analyses from a pooled cohort of the PARTNER trials, the FinnValve Registry, the Swedish Registry on Infective Endocarditis and the Danish National Patient Registry identified no difference in the incidence of IE over a follow-up period of between 5 and 44 months.[17-20] The incidence of IE after both TAVR and SAVR in our cohort is extremely low, and similar to the FinnValve (0.3 TAVR vs 0.3 SAVR, per 100 person-years) and PARTNER (0.5 TAVR vs 0.4 SAVR, per 100 person-years) estimates. The explanation for an apparent excess of IE cases after SAVR compared to TAVR in the UK population is unclear and requires further investigation. It is plausible that the risk of early-onset IE post TAVR might be less than for SAVR because of the lack of an open sternotomy wound and less need for invasive monitoring after the procedure.

We identified male sex as an independent baseline risk factor for the development of TAVR-IE. Male sex has previously been reported as a risk factor for IE following surgical aortic and mitral valve replacement using both mechanical and tissue valves.[22] Similarly, male sex has also been reported as a risk factor for TAVR-IE.[7,23] We found enterococci were the most frequent cause of TAVR-IE; enterococcal IE has been associated with older age and urological procedures.[24] Enterococci are an increasingly important cause of prostatitis,[25] raising the possibility that prostate disease may provide a possible mechanism for the increased risk in men. Enterococcal endocarditis presents an increasing challenge, given the development of high-level aminoglycoside resistance - it is therefore important that TAVR centres ensure that antibiotic prophylaxis regimens provide enterococcal coverage at the time of implant.[26]

Our analysis identified that annular valves (both mechanically-expandable and balloon-expandable) and an elevated post-deployment gradient are associated with an increased risk of TAVR-IE. Consistent with these findings, an elevated post-deployment gradient (> 15mmHg) has recently been identified as a risk factor for IE following transcatheter pulmonary valve implantation.[27] Elevated transvalvular gradients may lead to turbulent flow and endothelial damage, which then acts as a nidus for vegetation formation.[28] Mechanically-expandable and balloon-expandable valves were also associated with increased risk in our series. Previously, self-expanding valves have also been identified as a risk factor for TAVR-IE, and further studies of the risk associated with different valve designs are required to resolve this discordance.[6] We also identified a significant association between procedural general anaesthesia and subsequent IE. Although this did not retain statistical significance

within the multivariable model, oro-tracheal intubation has previously been identified as a risk factor for TAVR-IE.[6]

Oral streptococci accounted for 16.4% of cases in this series from the United Kingdom, but were isolated from only 3.6 - 6.9% in international series from countries where antibiotic prophylaxis is routinely prescribed to patients undergoing invasive dental procedures.[6-8] Only two TAVR-IE patient had dental procedures prior to presentation in our series, although in both cases IE was caused by oral streptococci. There remains significant controversy and ongoing uncertainty about the efficacy of antibiotic prophylaxis for prevention of IE. In addition, although dental evaluation (and dental extraction if indicated) prior to valve implantation remains the standard of care and standard practice for both TAVR and SAVR in the UK, it is also not supported by a clear evidence base.(29)

Our findings raise several questions for future research. Given the high rates of enterococcal IE, which commonly arises from the gastrointestinal or genitourinary tract, screening for underlying pathology (and excision of identified polyps or malignant lesions) might reduce the risk of bacteremia and subsequent IE. In light of the increased risk associated with elevated post-deployment gradient, there may be a role for aggressive pre-dilatation and improved valve sizing to minimize residual transvalvular gradient. Last, the optimal management of patients with TAVR-IE is unclear. Although very few patients in this cohort underwent surgical valve explantation, this was not associated with a statistically improved chance of survival at one year. Similarly, surgical intervention was not associated with survival benefit in a small recent cohort study reported by Mangner *et al*.[30]

Limitations

First, we used hospital discharge coding data to identify the majority of IE cases and there is a possibility that our incidence estimates are underestimates. Reported estimates for coding accuracy for infective endocarditis vary, with a range for sensitivity of 56-79% and specificity of 94-100%.(31,32). In our population, coding was performed independently by trained and accredited personnel and validated by receipt of individual patient data (obtained by review of the medical notes) in more than half of TAVR-IE cases. Second, for multivariable modeling, we cannot exclude the possibility of residual confounding accounting for our observations. Third, given the very substantial differences in the populations undergoing TAVR and SAVR during the period of our study, including both measured and unmeasured variables, we have elected to avoid propensity score matching but present the raw analyses. Finally, we were unable to obtain patient-level data for every identified case, resulting in incomplete data for some fields of interest.

CONCLUSIONS

Infective endocarditis is an important adverse outcome following TAVR, but may be less common than after SAVR. Clinicians should maintain a high level of concern in TAVR patients presenting with fever. Patients at increased risk of IE include men, those with mechanically-expanded or balloon-expandable valves, and patients with an elevated post-deployment transvalvular gradient. Mortality remains high. Research is required into novel strategies to translate insights into this condition into a reduction in incidence and adverse outcome.

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PERSPECTIVES

Competency in Medical Knowledge

There is a long-term risk of IE after TAVR that is associated with significant morbidity and mortality. The risk of IE after TAVR seems to be lower than after SAVR.

Competency in Patient Care

Patients undergoing TAVR should be made aware of the risk of IE following prosthetic valve implantation, the increased risk of infection following invasive procedures, the key symptoms of this condition, and the importance of seeking early medical attention.

Translational Outlook

Improved strategies are required for the prevention, diagnosis and management of IE after TAVR.

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FIGURE LEGENDS

FIGURE 1. Flowchart of the study cohort

FIGURE 2. Cumulative incidence of IE in patients after SAVR and TAVR

FIGURE 3. Kaplan-Meier curve showing 1-year overall survival in patients diagnosed with TAVR-IE (Central Illustration)

TABLES

TABLE 1: Baseline patient factors according to the occurrence of TAVR-IE

		IE	No IE	p-value
Age, mean (SD), y		79.2 (7.8)	81.3 (7.5)	0.003
Sex, n (%)	Male	107 (69.0%)	8331 (53.4%)	0.0002
	Female	48 (31.0%)	7103 (45.6%)	
Diabetes mellitus, n (%)	No	123 (78.8%)	11878 (76.7%)	0.522
	Yes	33 (21.2%)	3615 (23.3%)	
Smoking status, n (%)	Smoker	2 (2.3%)	442 (5.6%)	0.185
	Non-smoker	84 (97.7%)	7418 (94.4%)	
BMI, n (%)	>/=30	42 (27.8%)	3908 (26.3%)	0.68
	<30	109 (72.2%)	10936 (73.7%)	
Previous PCI, n (%)	Yes	26 (16.8%)	3172 (20.6%)	0.245
	No	129 (83.2%)	12253 (79.4%)	
Creatinine, μmol/L, median (IQR)		97 (78-124)	97 (80-120)	0.495
On dialysis, n (%)	Yes	0 (0.0%)	185 (1.6%)	0.123
	No	144 (100%)	11214 (98.4%)	
Pulmonary disease, n (%)	Yes	53 (34.0%)	4214 (27.4%)	0.069
	No	103 (66.0%)	11141 (72.6%)	

Severe liver disease, n (%)	Yes	1 (0%)	148 (1.3%)	0.519
	No	143 (99.3%)	11178 (98.7%)	
PVD, n (%)	Yes	34 (21.9%)	3437 (22.4%)	0.88
	No	121 (78.1%)	11878 (77.6%)	
Current/previous AF, n (%)	Yes	39 (26.0%)	3982 (26.5%)	0.89
	No	111 (74.0%)	11043 (73.5%)	
Previous cardiac surgery, n (%)	Yes	48 (30.6%)	4056 (25.8%)	0.176
	Previous CABG	30 (19.1%)	3180 (20.2%)	
	Previous valve	9 (5.7%)	644 (4.1%)	
	Both CABG & valve	9 (5.7%)	232 (1.5%)	
	No	109 (69.4%)	11652 (74.2%)	
PPM in-situ, n (%)	Yes	27 (17.4%)	3008 (19.9%)	0.437
	No	128 (82.6%)	12090 (80.1%)	
LES, median (IQR)		18.8 (10.8-25.4)	16.3 (10.7-25.7)	0.337
CSHA CFS score, n (%)	No/mild frailty	114 (80.9%)	9334 (83.2%)	0.456
	Mod/severe frailty	27 (19.1%)	1883 (16.8%)	

Abbreviations: AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CFS = clinical frailty scale; IE = infective endocarditis; IQR = interquartile range; LES = logistic Euroscore; Mod = moderate; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; PVD = peripheral vascular disease

TABLE 2: Baseline procedural factors according to the occurrence of TAVR-IE

		IE	No IE	p-value
LV function, n (%)	Normal	95 (62.5%)	9993 (65.3%)	0.469
	Impaired	57 (37.5%)	5308 (34.7%)	
Mitral regurgitation, n (%)	Mod-severe	28 (20.1%)	1842 (16.5%)	0.257
	None/mild	111 (79.9%)	9291 (83.5%)	
Periprocedural imaging, n (%)	TEE	80 (51.9%)	8219 (52.8%)	0.839
	No TEE	74 (48.1%)	7357 (47.2%)	
Procedure urgency, n (%)	Elective	136 (88.3%)	13195 (84.6%)	0.202
	Urgent	18 (11.7%)	2405 (15.4%)	
Anesthesia, n (%)	GA	83 (57.2%)	5217 (45.2%)	0.004
	Non-GA	62 (42.8%)	6336 (54.8%)	
BAV pre-TAVR, n (%)	Yes	16 (11.2%)	1055 (9.3%)	0.453
	No	127 (88.8%)	10229 (90.7%)	
Delivery approach, n (%)	Transfemoral	129 (84.3%)	12754 (82.8%)	0.612
	Non-transfemoral	24 (15.7%)	2657 (17.2%)	
Valve design, n (%)	Balloon-expandable	81 (52.0%)	8114 (53.6%)	0.001
	Self-expandable	47 (30.7%)	5795 (38.3%)	

	Mechanically-expandable	25 (16.3%)	1223 (8.1%)	
Post-deployment PG (mmHg)*	> median	68 (59.1%)	3790 (45.3%)	0.003
	</= median	47 (40.9%)	4583 (54.7%)	
Post-deployment AVA (cm^2) †	> median	45 (52.9%)	3047 (49.9%)	0.58
	</= median	40 (47.1%)	3059 (50.1%)	
Post-procedural AR, n (%) ‡	Yes	7 (5.1%)	439 (4.0%)	0.533
	No	131 (94.9%)	10475 (96.0%)	
Stroke prior to discharge, n (%)	Yes	2 (1.4%)	251 (2.3%)	0.487
	No	141 (98.6%)	10820 (97.7%)	
Vascular access site complication, n (%)	Yes	9 (6.4%)	904 (8.1%)	0.448
	No	132 (93.6%)	10201 (91.9%)	
Bleeding, n (%)	Yes	11 (7.7%)	960 (8.7%)	0.696
	No	131 (92.3%)	10107 (91.3%)	
AKI within 7 days, n (%)	Yes	8 (5.6%)	563 (5.1%)	0.786
	No	134 (94.4%)	10416 (94.9%)	
Drugs at discharge, n (%)	antithrombotic	50 (37.3%)	3145 (30.8%)	0.105
	no antithrombotic	84 (62.7%)	7065 (69.2%)	

antiplatelet	108 (80.0%)	8170 (80.7%)	0.827
no antiplatelet	27 (20.0%)	1948 (19.3%)	

Abbreviations: AKI = acute kidney injury; AR = aortic regurgitation; AVA = aortic valve area; BAV = balloon aortic valvuloplasty; IE = infective endocarditis; LV = Left ventricular; GA = general anesthesia; PG = peak gradient; TAVR = transcatheter aortic valve replacement; TEE = transesophageal echocardiogram

* median = 16.0 mmHg; † median = 1.77cm^2; ‡ ≥ moderate by echocardiography or angiography

TABLE 3: Multivariable analysis of factors associated with occurrence of TAVR-IE

	Hazard ratio	95% CI	p value
Age (per year)	0.98	0.96 - 1.00	0.07
Sex			
Male	2.05	1.35 - 3.11	0.001
Female	1 / referent		
Valve design			0.037
Balloon-expandable	1.60	1.01 - 2.52	0.045
Mechanically-expandable	2.15	1.16 - 4.01	0.015
Self-expandable	1 / referent		
Post-deployment PG (mmHg)			
> median	1.81	1.23 - 2.67	0.003
</= median	1 / referent		
General anesthesia	1.18	0.79 - 1.78	0.42
Pulmonary disease	1.27	0.86 - 1.89	0.23

Abbreviations: CI = confidence interval; PG = peak gradient

TABLE 4: Microbiology of TAVR-IE & prior invasive procedures

Micro-organism	**n (%)**
	n = 85
Enterococci	22 (25.9)
Oral group streptococci	14 (16.4)
Staphylococcus aureus	10 (11.8)
Streptococcus gallolyticus (*Streptococcus bovis*)	8 (9.4)
Coagulase negative staphylococci	7 (8.2)
Culture negative	7 (8.2)
Non-HACEK Gram negative	5 (5.9)
Other	17 (20.0)

Invasive procedure in 3 months prior to IE	**n (%)**
	n = 85
TAVR	5 (5.9)
Endoscopy	4 (4.7)
Orthopaedic	3 (3.5)
Urological	2 (2.4)
Dental	2 (2.4)
Cardiac device implantation	2 (2.4)
Vascular access	2 (2.4)
Other	1 (1.2)
Total	21 (24.7)

Abbreviations: HACEK = Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella; IE = infective endocarditis; TAVR = transcatheter aortic valve replacement

TABLE 5: Echocardiographic findings in TAVR-IE

Echocardiographic finding	**TTE (n, %)** n=78	**TEE (n, %)** n=51
TAVR valve leaflet vegetations	8 (10.3)	30 (58.8)
TAVR valve stent frame vegetations	2 (2.6)	5 (9.8)
Mitral valve vegetations	7 (8.9)	6 (11.8)
Tricuspid valve vegetations	1 (1.3)	1 (2.0)
Other vegetations	3 (3.9)	7 (13.7)
Peri-annular complications	2 (2.6)	7 (13.7)
New paravalvular aortic regurgitation	13 (16.7)	9 (17.6)
New transvalvular aortic regurgitation	3 (3.9)	0 (0)
New mitral regurgitation	6 (7.7)	5 (9.8)
Mean gradient across TAVR valve (mmHg)	17.1	17.5

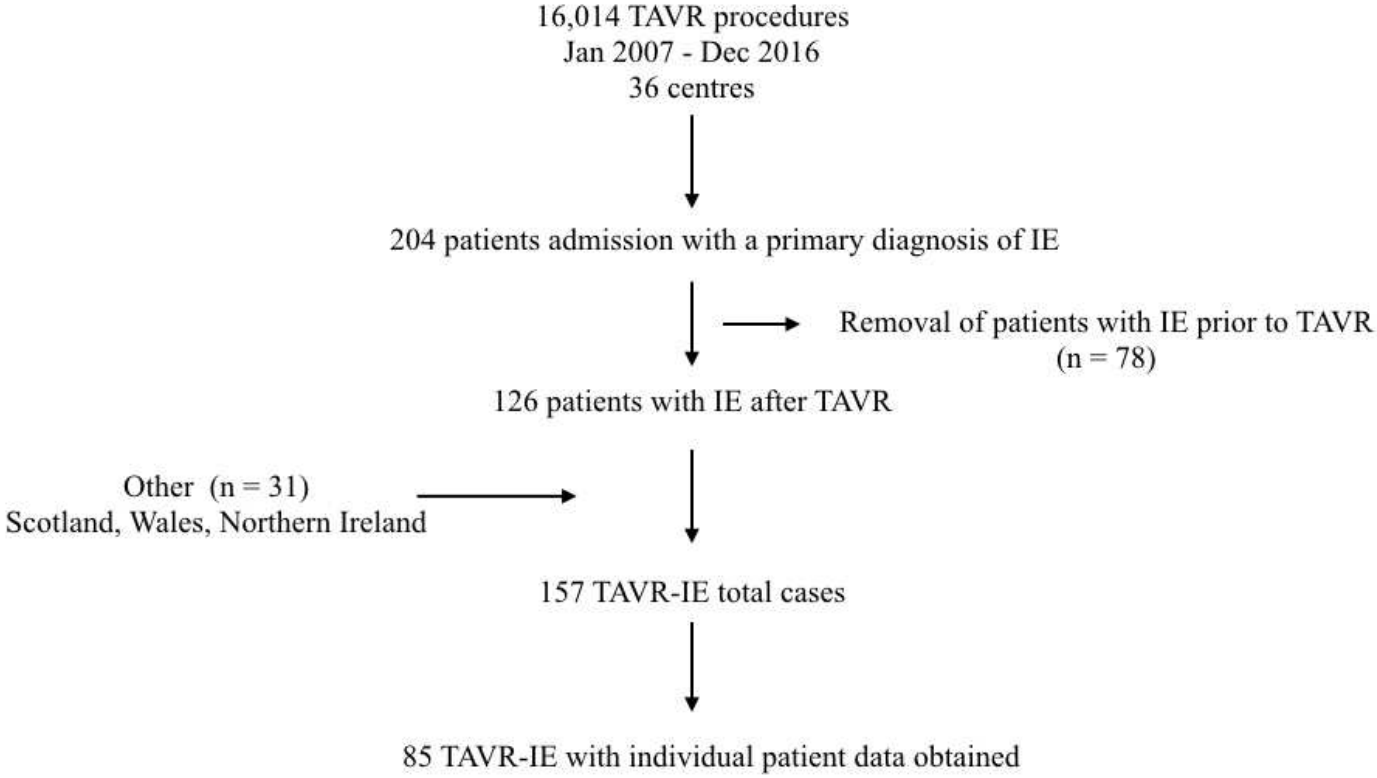
Abbreviations: TEE = transesophageal; TTE = transthoracic; TAVR = transcatheter aortic valve replacement

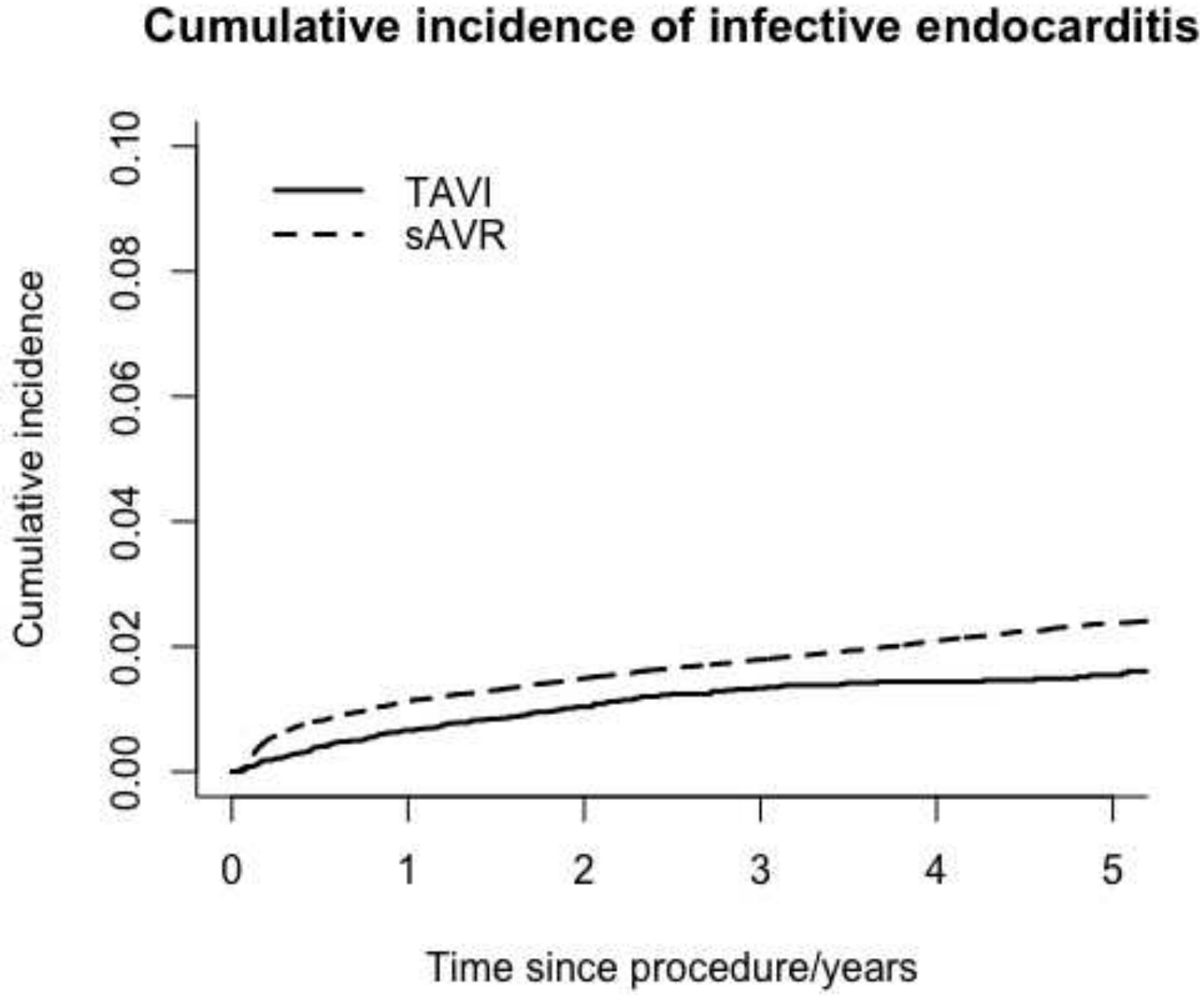
TABLE 6: Complications of TAVR-IE

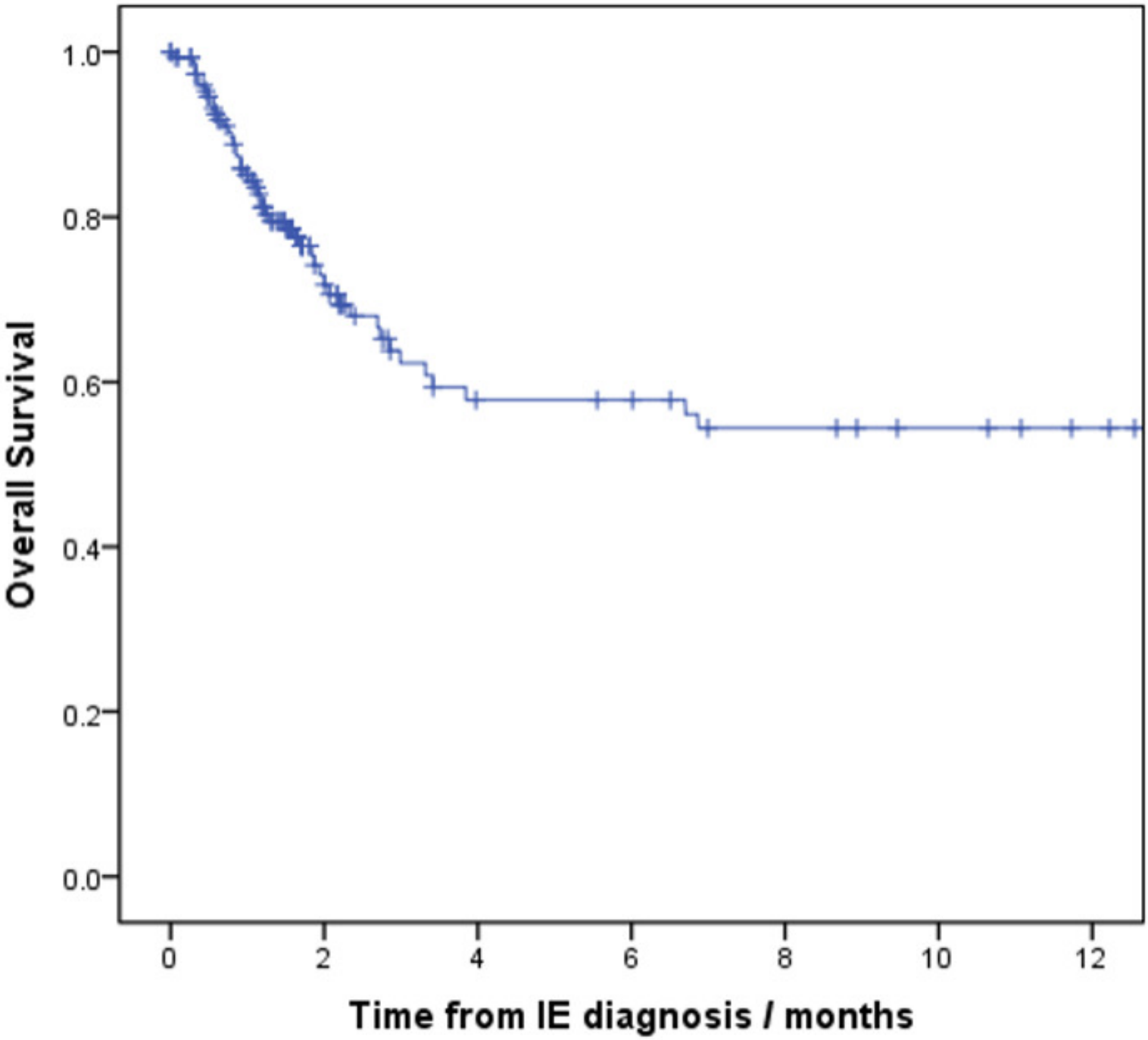
Complication	n (%) n = 85
Acute kidney injury	17 (20)
Systemic emboli	13 (15.3)
Pulmonary oedema	13 (15.3)
Ischaemic stroke	9 (10.6)
Cardiogenic shock	9 (10.6)
Septic shock	7 (8.2)
Persistent bacteraemia	4 (4.7)
Periannular abscess	4 (4.7)
Haemorrhagic stroke	2 (2.4)
Valve dehiscence	2 (2.4)
Vegetation greater than 15mm in size	0 (0)

TABLE 7: Multivariable analysis of factors associated with death following TAVR-IE

	Hazard ratio	95% CI	p valu
Age (per year)	1.05	0.99-1.10	0.089
Sex			
Male	1.38	0.65-2.91	0.402
Female	1 / referent		
Cardiogenic shock			
Yes	2.98	1.17-7.55	0.022
No	1 / referent		
Septic shock			
Yes	4.71	1.13-11.74	0.03
No	1 / referent		
Stroke			
Yes	5.29	1.25-15.88	0.021
No	1 / referent		


16,014 TAVR procedures
Jan 2007 - Dec 2016
36 centres
204 patients admission with a primary diagnosis of IE
Removal of patients with IE prior to TAVR
(n = 78)
126 patients with IE after TAVR
Other (n = 31)
Scotland, Wales, Northern Ireland
157 TAVR-IE total cases
85 TAVR-IE with individual patient data obtained


Cumulative incidence of infective endocarditis
Cumulative incidence
0.00
0.02
0.04
0.06
0.08
0.10
TAVI
sAVR
0
1
2
3
4
5
Time since procedure/years



At risk:

157	62	37	36	31	28	25