Original research

Risk of infective endocarditis after surgical and transcatheter aortic valve replacement

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ABSTRACT

Objective To define the incidence and risk factors for infective endocarditis (IE) following surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).

Methods All patients who underwent first SAVR or TAVI in England between 2007 and 2016 were identified from the NICOR databases. Hospital admissions with a primary diagnosis of IE were identified by linkage with the NHS Hospital Episode Statistics database. Approval was obtained from the NHS Research Ethics Committee.

Results 2057 of 91 962 patients undergoing SAVR developed IE over a median follow-up of 53.9 months—an overall incidence of 4.81 [95% CI 4.61 to 5.03] per 1000 person-years. Correspondingly, 140 of 14 195 patients undergoing TAVI developed IE over a median follow-up of 24.5 months—an overall incidence of 3.57 [95% CI 3.00 to 4.21] per 1000 person-years. The cumulative incidence of IE at 60 months was higher after SAVR than after TAVI (2.4% [95% CI 2.3 to 2.5] vs 1.5% [95% CI 1.3 to 1.8], HR 1.60, p<0.001). Across the entire cohort, SAVR remained an independent predictor of IE after multivariable adjustment. Risk factors for IE included younger age, male sex, atrial fibrillation, and dialysis.

Conclusions IE is a rare complication of SAVR and TAVI. In our population, the incidence of IE was higher after SAVR than after TAVI.

INTRODUCTION

Infective endocarditis (IE) is a life-threatening complication of prosthetic valve replacement which affects approximately 3–10 per 1000 person-years.[1 2] In the last 15 years, transcatheter aortic valve implantation (TAVI) has revolutionised the treatment of aortic stenosis, 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] and this risk may be even higher in elderly patients undergoing frequent hospitalisation and invasive medical procedures.[4]

To date, few studies have systematically evaluated the population risk of IE after TAVI and SAVR over long-term follow-up. Insights concerning risk factors for IE have largely been limited to registry studies and clinical trial populations with attendant selection bias or incomplete follow-up.[5–8] There is ongoing uncertainty as to which patients with prosthetic valves are most susceptible to IE and how to reduce this risk.[9] Unlike in Europe and the USA, routine oral antibiotic prophylaxis for at-risk patients undergoing invasive dental procedures has not been recommended in the UK since 2008.[10 11]

In this study, we use linked national registry data to provide insights into the epidemiology of IE following TAVI (TAVI-IE) and surgical aortic valve replacement (SAVR-IE) in England. The primary aims were (1) to understand the relative incidence of IE after SAVR and TAVI, and (2) to determine the risk factors for developing IE in each population.

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 TAVI or SAVR in England. Ethical approval for the study was provided by the London Bromley Research Ethics Committee (reference 16/LO/0275) and the National Health Service confidentiality advisory group (reference 17CAG0001).

Study populations

All patients undergoing first TAVI or SAVR (±coronary artery bypass grafting, CABG) between 1 January 2007 and 31 December 2016 in England were identified from the National Institute for Cardiovascular Outcomes Research (NICOR) TAVI and Adult Cardiac Surgery databases, respectively. These data are submitted by implanting clinical teams, with case ascertainment performed centrally by NICOR.[12] We extracted data concerning baseline patient demographics (age, sex), comorbidities (smoking, atrial fibrillation, previous percutaneous coronary intervention, kidney disease, lung disease, prior cardiac surgery) and key procedural variables for TAVI (valve type, post-deployment hemodynamics) and SAVR (valve type, procedural urgency, concurrent CABG). Patients undergoing repeat SAVR or valve-in-valve TAVI were excluded.

Cases

The National Health Service (NHS) records a primary discharge diagnosis using the ICD-10

Linked

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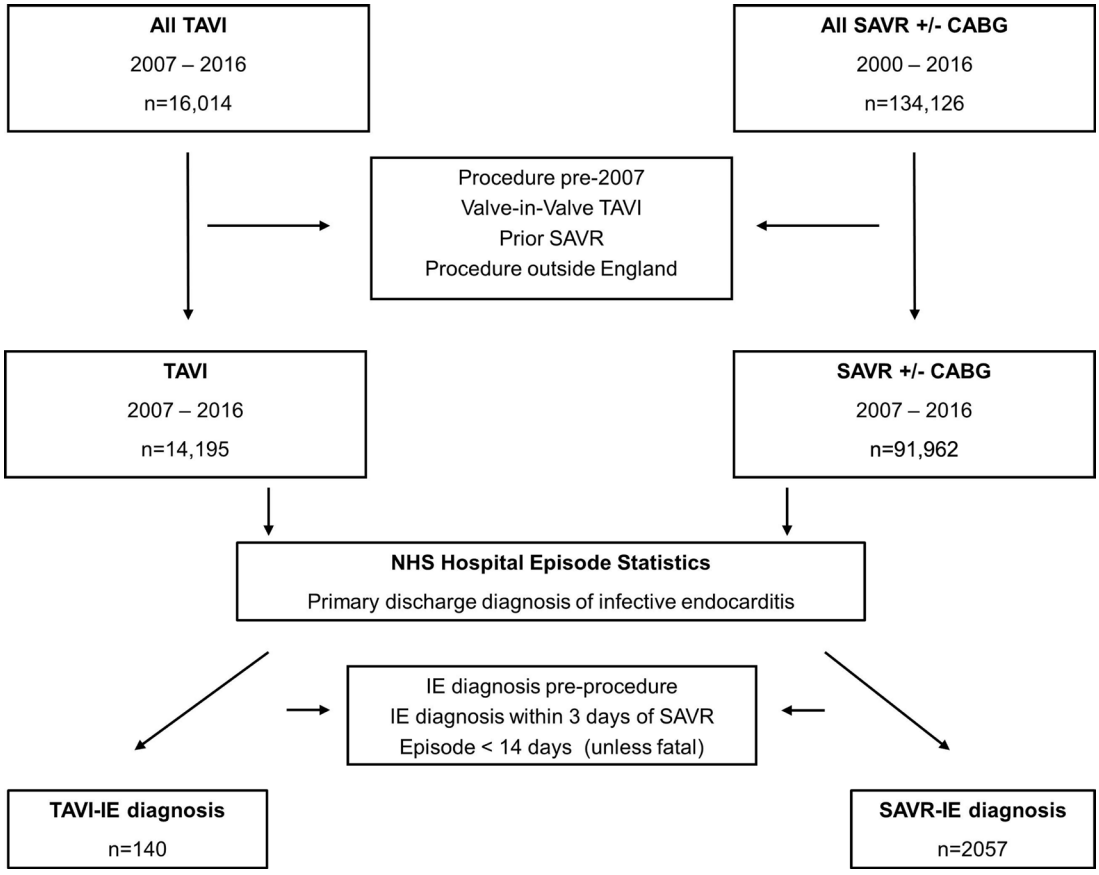

Figure 1 Flowchart of the study cohorts.

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 hospitalised 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 1 May 2017 (figure 1). 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).

All patients with a known episode of IE (based on HES APC episodes, from 1999 onwards) prior to first SAVR or TAVI were excluded from the analysis. The first admission with IE after SAVR/TAVI was used to calculate time to IE. To reduce the possibility of including cases where SAVR may have been undertaken for the treatment of IE, the diagnosis of SAVR-IE had to be established a minimum of 72 hours after the time of surgery. Only first admissions were included: 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. Only admissions of ≥14 days' duration were included, unless fatal, to improve the specificity of the diagnosis.

Outcomes

The primary outcome was the incidence of IE during follow-up, analysed as cumulative incidence and incidence rate per 1000 person-years.

Statistical analysis

Continuous data are expressed as mean±SD or median with IQR. Categorical data are presented as absolute number with percentage. Comparison between groups was performed using the Fisher exact or χ^2 test for categorical variables (with Fisher exact used preferentially), 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 elimination model was used to identify significant risk factors, and independent variables with p value >0.1 were sequentially excluded. Also, 95% CIs were calculated. Missing data were assumed to be missing completely at random. Patients with ≥10% missing data for the covariate of interest were excluded. Where there was <10% missing data, imputation was performed for the multivariable model using a Markov chain Monte Carlo approach implemented in SPSS. Data were analysed with SPSS V.22.0 and R V.3.6.3 (R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

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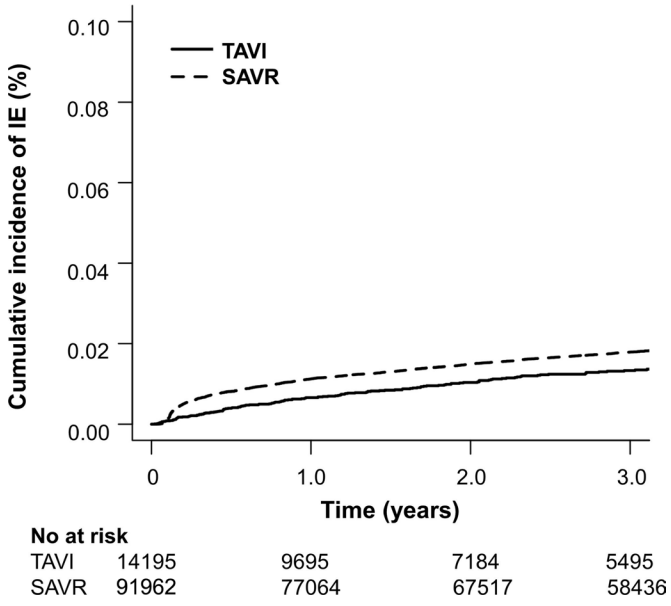

Figure 2 Cumulative incidence of IE in patients after surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI).

RESULTS

Incidence of IE after SAVR and TAVI

Between 1 January 2007 and 31 December 2016, a total of 14 195 TAVI and 91 962 SAVR procedures were performed across England (figure 1). As anticipated, there were significant differences in the demographics of patients undergoing TAVI and SAVR (online supplemental table 1). Patients undergoing TAVI had a median age of 83.0 (IQR 77.0–86.0) years, compared with a median age of 72.0 (IQR 63.9–78.1) in the SAVR cohort (p<0.0001). The TAVI cohort had a significantly higher surgical risk (median logistic Euroscore 16.1 [IQR 10.7–25.3] vs 5.8 [IQR 3.3–10.1)], p<0.001). In the SAVR cohort, 33,527/92,961 (36.1%) underwent concomitant coronary artery bypass grafting (CABG) and 7202/92,961 (7.7%) underwent greater than one valve intervention.

There were 2057 cases of IE after SAVR (SAVR-IE) over a median follow-up of 53.9 (IQR 22.3–88.8) months, giving an incidence rate of 4.81 (95% CI 4.61 to 5.03) per 1000 per-years (figure 2). In comparison, there were 140 cases of IE after TAVI (TAVI-IE) over a median follow-up of 24.5 (IQR 8.2–54.0) months, corresponding to an incidence rate of 3.57 (95% CI 3.00 to 4.21) per 1000 person-years. The cumulative incidence of IE at 60 months was 2.4% (95% CI 2.3% to 2.5%) for SAVR compared with 1.5% (95% CI 1.3 to 1.8) for TAVI (HR 1.6, p<0.001; figure 2). The median time to IE was 12.9 (IQR 1.78–42.0) months after SAVR and 10.15 (IQR 4.05–21.7) months after TAVI. The distribution of time to IE following SAVR and TAVI is shown in online supplemental figure 1.

Patient demographics according to the presence of IE are shown in table 1. For both SAVR and TAVI, patients with IE were younger (TAVI: 81.5 [IQR 75.8–85.0] vs 83.0 [IQR 77.0–86.0], p=0.02; SAVR: 69.5 [IQR 59.5–76.6] vs 72.0 [IQR 64.0–78.2], p<0.0001) and a higher proportion of IE cases occurred in males (TAVI 69.3% vs 53.3%, p=0.0002; SAVR 71.4% vs 63.7%, p<0.0001). In the SAVR cohort, patients with IE were more likely to be on dialysis, have a history of prior PCI, smoking or atrial fibrillation, have impaired LV function and had a higher logistic Euroscore. There was no difference in the proportion of patients with SAVR-IE according to valve type (p=0.2). Concomitant CABG was associated with a lower rate of IE (29.0% vs 36.6%, p<0.0001).

Risk factors for IE after TAVI

In patients undergoing TAVI, Cox regression modelling was performed to identify baseline clinical and procedural factors associated with subsequent IE. On univariable analysis, younger age, male sex, valve design and increasing post-deployment peak gradient were associated with subsequent TAVI-IE (table 2). Factors which retained statistical significance on multivariable analysis were younger age (per year, HR 0.98, 95% CI 0.96 to 0.99, p=0.01), male sex (HR 1.83, 95% CI 1.26 to 2.64, p=0.001), implantation of a mechanically expandable valve (compared with self-expandable valve, HR 3.14 [95% CI 1.85 to 5.35], p<0.001) and increasing residual peak gradient after TAVI (per mmHg, HR 1.002 [95% CI 1.00 to 1.005], p=0.04).

Risk factors for IE after SAVR

In patients undergoing SAVR, Cox regression modelling was performed to identify baseline factors associated with subsequent IE. On univariable analysis, younger age, male sex, current smoking, elevated body mass index (BMI >30 kg/m^2), atrial fibrillation, higher serum creatinine, current dialysis, elevated logistic Euroscore (greater than the median) and non-elective surgery were associated with subsequent SAVR-IE (table 3). On multivariable analysis, factors that retained statistical significance as predictors of IE were younger age (per year, HR 0.97, 95% CI 0.97 to 0.98, p<0.001), male sex (HR 1.39, 95% CI 1.21 to 1.60, p<0.001), elevated BMI (1.13, 95% CI 0.99 to 1.29, p<0.01), atrial fibrillation (HR 1.30, 95% CI 1.09 to 1.54, p<0.01), current dialysis (HR 2.36, 95% CI 1.13 to 4.97, p=0.03), elevated logistic Euroscore (HR 1.88, 95% CI 1.64 to 2.15, p=0.02) and a non-elective procedure (HR 2.19, 95% CI 1.92 to 2.48, p<0.01). Concomitant CABG was associated with a lower risk of future IE (HR 0.64, 95% CI 0.56 to 0.74, p<0.01).

Risk factors for IE across all patients undergoing aortic valve replacement

Across the entire cohort undergoing aortic valve replacement by TAVI or SAVR (n=106 157), there was an increased risk of IE in patients undergoing SAVR on univariate analysis (HR 1.65, 95% CI 1.39 to 1.96, p<0.001). The increased risk of IE in patients undergoing SAVR was consistent across subgroups, although a significant interaction was identified with procedural urgency and renal function (online supplemental file 3). Multivariable analysis was then performed, with procedural urgency treated as an interaction term (table 4). Creatinine was excluded from the multivariable analysis due to additional interaction with dialysis. On multivariable analysis, factors which retained statistical significance as predictors of IE were younger age (per year, HR 0.98, 95% CI 0.98 to 0.99, p<0.001), male sex (HR 1.30, 95% CI 1.17 to 1.44, p<0.001), atrial fibrillation (HR 1.39, 95% CI 1.23 to 1.58, p<0.001), higher logistic Euroscore (per point, HR 1.004, 95% CI 1.000 to 1.001, p=0.01), and both elective SAVR (HR 1.86, 95% CI 1.23 to 2.83, p=0.003) and urgent SAVR (HR 3.54, 95% CI 2.33 to 5.38, p<0.001) compared with elective TAVI.

DISCUSSION

The key findings of this study are as follows: (1) in an unselected consecutive nationwide population over long-term follow-up, the

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Table 1 Baseline patient and procedural factors according to the occurrence of infective endocarditis

	TAVI (N=14 195)		SAVR (N=91 962)	
	IE (n=140)	No IE (n=14 055)	IE (n=2057)	No IE (89 905)
Age, median (IQR), years	81.5 (75.8–85.0)	83.0 (77.0–86.0)	69.5 (59.5–76.6)	72.0 (64.0–78.2)
Sex, n (%)				
Male	97 (69.3%)	7498 (53.3%)	1468 (71.4%)	57 267 (63.7%)
Female	41 (29.3%)	6277 (44.7%)	589 (28.6%)	32 633 (36.3%)
NK	2 (1.4%)	280 (2.0%)	0 (0%)	5 (0%)
BMI, n (%)				
≥30	34 (24.3%)	3520 (25.0%)	699 (34.0%)	28 849 (32.1%)
<30	100 (71.4%)	9696 (69.0%)	1287 (62.5%)	57 427 (63.9%)
NK	6 (4.3%)	839 (6.0%)	72 (4.0%)	3628 (3.5%)
DM, n (%)				
No	108 (77.1%)	10 490 (74.6%)	1678 (81.5%)	72 723 (80.9%)
Yes	31 (22.1%)	3209 (22.8%)	282 (13.7%)	13 416 (14.9%)
NK	1 (0.7%)	356 (2.5%)	98 (4.8%)	3765 (4.2%)
Creatinine, median, µmol/L (IQR)	97.0 (80.0–117.8)	97.0 (78.0–123.0)	89.0 (75.0–110.0)	85.0 (73.0–103)
On dialysis, n (%)				
Yes	0 (0%)	158 (1.1%)	20 (1%)	222 (0.2%)
No	132 (94.3%)	9725 (69.2%)	976 (47.4%)	35 844 (39.9%)
NK	8 (5.7%)	4172 (29.7%)	1062 (51.6%)	53 838 (59.9%)
Previous PCI, n (%)				
Yes	21 (15.0%)	2718 (19.3%)	88 (4.3%)	4841 (5.4%)
No	117 (83.6%)	10 910 (77.6%)	1903 (92.5%)	82 541 (91.8%)
NK	2 (1.4%)	427 (3.0%)	67 (3.2%)	2522 (2.8%)
Smoking, n (%)				
Yes	2 (1.4%)	407 (2.9%)	188 (9.1%)	6880 (7.7%)
No	73 (52.1%)	6521 (46.4%)	1846 (89.7%)	82 328 (91.7%)
NK	65 (46.4%)	7127 (50.7%)	24 (1.2%)	696 (0.7%)
Pulmonary disease, n (%)				
Yes	48 (34.3%)	3678 (26.2%)	289 (14.0%)	14 013 (15.6%)
No	91 (65.0%)	9884 (70.3%)	1758 (85.4%)	75 446 (83.9%)
NK	1 (0.7%)	493 (3.5%)	11 (0.5%)	445 (0.5%)
History of AF, n (%)				
Yes	36 (25.7%)	3444 (24.5%)	301 (14.6%)	11 508 (12.8%)
No	97 (69.3%)	9785 (69.6%)	1587 (77.1%)	72 751 (80.9%)
NK	7 (5%)	826 (5.9%)	170 (8.3%)	5645 (6.3%)
Previous cardiac surgery, n (%)				
Yes	44 (31.4%)	3549 (25.2%)	91 (4.4%)	3620 (4.0%)
No	96 (68.6%)	10 357 (73.7%)	1846 (89.7%)	78 183 (87.0%)
NK	0 (0%)	126 (0.9%)	121 (5.9%)	8108 (9.0%)
PPM, n (%)				
Yes	27 (19.3%)	2661 (18.9%)	35 (1.7%)	1589 (1.8%)
No	111 (79.3%)	10 670 (75.9%)	1853 (90.0%)	82 670 (92.0%)
NK	2 (1.4%)	724 (5.2%)	170 (8.3%)	5645 (6.3%)
LV function, n (%)				
Normal	84 (60.0%)	8861 (63.0%)	1439 (70.0%)	66 456 (74.0%)
Impaired	51 (36.4%)	4647 (33.1%)	604 (29.4%)	22 923 (25.5%)
NK	5 (3.6%)	547 (3.9%)	14 (0.7%)	525 (0.6%)
Procedure urgency, n (%)				
Elective	127 (90.7%)	11 921 (84.8%)	1304 (63.4%)	68 759 (76.5%)
Urgent	10 (7.1%)	1883 (13.4%)	752 (36.6%)	21 106 (23.5%)
NK	3 (2.1%)	251 (1.8%)	1 (0.04%)	35 (0.03%)
Logistic Euroscore (IQR)	18.82 (11.0–25.4)	16.09 (10.7–25.3)	6.19 (3.5–11.7)	5.8 (3.3–10.1)
TAVI valve, n (%)				
BE	75 (53.6%)	7327 (52.1%)		
SE	39 (27.9%)	4930 (35.1%)		
ME	22 (15.7%)	1154 (8.2%)		

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Table 1 Continued

	TAVI (N=14 195)		SAVR (N=91 962)	
	IE (n=140)	No IE (n=14 055)	IE (n=2057)	No IE (89 905)
NK	4 (2.9%)	644 (4.6%)		
SAVR valve, n (%)				
Bio			1595 (77.5%)	70 883 (78.8%)
Mech			432 (21.0%)	17 417 (19.4%)
NK			30 (1.5%)	1604 (1.8%)
Concomitant CABG, n (%)				
No			1461 (71.0%)	56 940 (63.3%)
Yes			595 (29.0%)	32 932 (36.6%)
NK			1 (0.0%)	32 (0.0%)

AF, atrial fibrillation; BE, balloon expandable; Bio, bioprosthetic; BMI, body mass index; CABG, coronary artery bypass grafting; IE, infective endocarditis; LV, left ventricular; ME, mechanically expandable; Mech, mechanical; NK, not known; PCI, percutaneous coronary intervention; PPM, permanent pacemaker.

risk of IE following SAVR was 4.81 per 1000 person-years, and after TAVI was 3.57 per 1000 person-years; (2) this difference in the incidence of SAVR-IE and TAVI-IE was small but statistically significant, with SAVR remaining an independent predictor of IE across the entire cohort; (3) risk factors for IE among all patients undergoing aortic valve replacement (SAVR or TAVI) included younger age, male sex, atrial fibrillation, dialysis and an elevated logistic Euroscore; (4) specific risk factors for TAVI-IE included patients with mechanically expandable valves and those with an elevated post-deployment residual gradient.

Table 2 Cox regression analysis of factors associated with occurrence of TAVI-IE

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (per year)	0.97	0.95 to 0.99	0.003	0.98	0.96 to 1.00	0.013
Male sex	2.01	1.40 to 2.90	<0.001	1.83	1.26 to 2.64	0.001
Diabetes mellitus	1.06	0.71 to 1.58	0.784			
Current smoker	2.32	0.57 to 9.46	0.240			
BMI>30	1.04	0.71 to 1.54	0.844			
Pulmonary disease	1.39	0.98 to 1.98	0.063			
Severe liver disease	1.89	0.26 to 13.5	0.526			
History of AF	1.12	0.76 to 1.64	0.576			
Previous cardiac surgery	1.15	0.81 to 1.64	0.443			
BAV pre-TAVI	1.13	0.65 to 1.97	0.664			
Previous PCI	0.72	0.45 to 1.14	0.157			
PPM in situ	1.01	0.66 to 1.53	0.974			
CSHA CFS moderate/severe frailty	1.24	0.80 to 1.90	0.336			
Mitral regurgitation (≥moderate)	1.14	0.73 to 1.78	0.564			
Impaired LV function	1.07	0.76 to 1.52	0.694			
Logistic Euroscore (>median)	1.14	0.68 to 1.92	0.614			
Valve design			<0.001			<0.001
Self-expandable	–	–	–	–	–	–
Balloon expandable	1.38	0.93 to 2.03	0.106	1.40	0.95 to 2.06	0.089
Mechanically expandable	3.24	1.90 to 5.51	<0.001	3.14	1.85 to 5.35	<0.001
Procedural factors						
Procedure urgency (non-elective)	0.55	0.29 to 1.05	0.070	0.54	0.28 to 1.02	0.059
General anaesthesia	1.09	0.76 to 1.57	0.633			
Non-transfemoral delivery	0.69	0.44 to 1.09	0.110			
Post-deployment PG (per mmHg)	1.002	1.000 to 1.005	0.027	1.002	1.00 to 1.005	0.040
Post-deployment AVA (cm^2) ≤median	1.16	0.73 to 1.84	0.530			
Post-procedural AR*	1.19	0.55 to 2.55	0.659			
Stroke prior to discharge	0.76	0.19 to 3.06	0.695			
Vascular access site complication	0.77	0.39 to 1.52	0.452			
Bleeding	0.91	0.49 to 1.68	0.752			
AKI within 7 days	1.36	0.66 to 2.78	0.401			

*≥Moderate by echo or angiography.
AF, atrial fibrillation; AKI, acute kidney injury; AR, aortic regurgitation; AVA, aortic valve area; BAV, balloon aortic valvuloplasty; BMI, body mass index; CABG, coronary artery bypass grafting; CFS, Clinical Frailty Scale; GA, general anaesthesia; IE, infective endocarditis; LV, left ventricular; Mod, moderate; PCI, percutaneous coronary intervention; PG, peak gradient; PPM, permanent pacemaker; PVD, peripheral vascular disease; TAVI, transcatheter aortic valve implantation; TEE, trans-oesophageal echocardiogram.

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Table 3 Cox regression analysis of factors associated with SAVR-IE

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (per year)	0.98	0.98 to 0.98	<0.001	0.97	0.97 to 0.98	<0.001
Male sex	1.42	1.29 to 1.56	<0.001	1.39	1.21 to 1.60	<0.001
Diabetes mellitus	0.95	0.84 to 1.08	0.412			
Current smoker	1.24	1.07 to 1.44	0.005	1.10	0.89 to 1.35	0.380
BMI>30	1.11	1.01 to 1.21	0.031	1.13	0.99 to 1.29	0.003
Pulmonary disease	0.91	0.81 to 1.04	0.155			
History of AF	1.22	1.09 to 1.38	0.001	1.30	1.09 to 1.54	0.003
Previous cardiac surgery	1.05	0.85 to 1.30	0.651			
Previous PCI	0.85	0.68 to 1.05	0.123			
PPM in situ	1.05	0.75 to 1.46	0.785			
Creatinine	1.002	1.002 to 1.003	<0.001			
On dialysis	3.71	2.38 to 5.78	<0.001	2.36	1.13 to 4.97	0.027
Impaired LV function	1.20	1.09 to 1.32	<0.001	1.01	0.88 to 1.16	0.892
Logistic Euroscore>median	1.15	1.05 to 1.26	0.002	1.88	1.64 to 2.15	0.023
Valve design (mechanical)	0.95	0.86 to 1.06	0.383			
Procedural factors						
Procedure urgency (non-elective)	1.97	1.80 to 2.16 s	<0.001	2.19	1.92 to 2.48	0.001
Concurrent CABG	0.71	0.62 to 0.80	<0.001	0.64	0.56 to 0.74	0.002

AF, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass grafting; IE, infective endocarditis; LV, left ventricular; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; TAVI, transcatheter aortic valve implantation.

Incidence of IE following SAVR and TAVI

Several prior studies have compared the incidence of IE after SAVR and TAVI (table 5).[13–18] Observational analyses using the United States Readmissions Database,[13] Danish National Patient Registry,[14] the FinnValve Registry[15] and a pooled analysis from the PARTNER trials[16] identified no difference in the incidence of IE over a follow-up period of 5–44 months. A large study of 107 786 patients in France identified a numerically higher incidence of IE after TAVI compared with SAVR, but this difference was not statistically significant after propensity score matching.[17] In contrast, a pooled analysis from three randomised controlled trials of the self-expanding CoreValve transcatheter heart valve family against SAVR reported a higher cumulative incidence of IE after SAVR compared with TAVI over a mean follow-up of approximately 2 years.[18]

The incidence of IE after SAVR and TAVI in our cohort was extremely low and similar to incidence derived from pooled analyses of the PARTNER[16] and CoreValve trials,[18] in which patients had an adjudicated diagnosis of IE. The mechanisms behind an apparent excess of IE cases after SAVR compared with TAVI seen in our cohort (and the CoreValve trials) are currently unclear and require further investigation. One possible explanation is

Table 4 Cox regression analysis of factors associated with IE for all patients undergoing SAVR or TAVI

	Univariable			Multivariable		
Variable	**HR**	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age (per year)	0.98	0.98 to 0.98	<0.001	0.98	0.98 to 0.99	<0.001
Male sex	1.48	1.35 to 1.62	<0.001	1.30	1.17 to 1.44	<0.001
Diabetes mellitus	0.93	0.82 to 1.05	0.219			
Current smoker	1.22	1.05 to 1.42	0.009	1.09	0.93 to 1.28	0.277
BMI>30	1.11	1.02 to 1.22	0.020			
Pulmonary disease	0.93	0.82 to 1.04	0.193			
History of AF	1.17	1.04 to 1.31	0.009	1.39	1.23 to 1.58	<0.001
Previous PCI	0.75	0.62 to 0.91	0.003	0.91	0.74 to 1.13	0.387
PPM in situ	0.84	0.65 to 1.08	0.177			
Creatinine*	1.002	1.001 to 1.002	<0.001			
On dialysis	2.76	1.78 to 4.30	<0.001	2.05	1.33 to 3.18	0.002
Impaired LV function	1.17	1.07 to 1.28	0.001	1.03	0.93 to 1.14	0.638
Logistic Euroscore	1.001	1.000 to 1.001	<0.001	1.0004	1.000 to 1.001	0.005
Procedure						
Elective TAVI	Ref		<0.001	Ref		
Urgent TAVI	0.55	0.29 to 1.06	0.073	1.11	0.38 to 3.21	0.848
Elective SAVR	1.29	1.08 to 1.55	0.006	1.86	1.23 to 2.83	0.003
Urgent SAVR	2.55	2.11 to 3.08	<0.001	3.54	2.33 to 5.38	<0.001

*Creatinine not included in multivariable analysis due to significant interaction with dialysis.
AF, atrial fibrillation; BMI, body mass index; LV, left ventricle; PPM, permanent pacemaker; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

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Table 5 Summary of studies comparing the incidence of infective endocarditis after SAVR or TAVI

Study	Population	Follow-up time	Incidence of SAVR-IE	Incidence of TAVI-IE	Comment
Lanz *et al* 2021[18]	Total 4077 patients pooled from three multicentre RCTs comparing TAVI (using devices of the self-expanding CoreValve family) with SAVR, and SURTAVI continued access registry N=1828 SAVR N=2249 TAVI	Mean follow-up: SAVR 2.17 (±1.54) years TAVI 2.15 (±1.49) years	5.28 (95% CI 3.02 to 7.54) per 1000 patient-years Cumulative incidence 1.58% (95% CI 0.97 to 2.46) at 5 years	2.47 (95% CI 1.07 to 3.87) per 1000 patient-years Cumulative incidence 1.01% (95% CI 0.47 to 1.96) at 5 years	Higher cumulative incidence of IE after SAVR (p=0.047)
Fauchier *et al* 2020[17]	Total 107 786 patients identified from French national database N=60 253 SAVR N=47 533 TAVI	Mean follow-up: 2.0 years	14.0 (95% CI 13.4 to 14.6) per 1000 patient-years	18.9 (95% CI 17.8 to 20.0) per 1000 patient-years	In unmatched population, risk of IE higher after TAVI vs SAVR (RR 1.35, 95% CI 1.26 to 1.45). After propensity score matching, no significant difference in the incidence of TAVI-IE and SAVR-IE (RR 1.09, 95% CI 0.96 to 1.23)
Summers *et al* 2019[16]	Total 8530 patients pooled from PARTNER 1 and PARTNER 2 trials and registries N=1257 SAVR N=7273 TAVI	Mean follow-up: 2.69 (±1.55) years	4.10 (95% CI 2.33 to 7.22) per 1000 person-years	5.21 (95% CI 4.26 to 6.38) per 1000 person-years	No significant difference in incidence of TAVI-IE and SAVR-IE—incidence rate ratio 1.27 (95% CI 0.70 to 2.32); p=0.44
Butt *et al* 2019[14]	Total 6409 patients identified from the Danish National Patient Registry N=3777 SAVR N=2632 TAVI	Mean follow-up: 3.6 years	12 (95% CI 10 to 14) per 1000 person-years Cumulative incidence 5.1% (95% CI 4.4 to 6.0) at 5 years	16 (95% CI 14 to 19) per 1000 person-years Cumulative incidence 5.8% (95% CI 4.7 to 7.0) at 5 years	No significant difference in the risk of TAVI-IE and SAVR-IE by multivariable CPH analysis (HR 1.12, 95% CI 0.84 to 1.49)
Moriyama *et al* 2019[15]	Total 6463 patients identified from the FinnValve Registry. N=4333 SAVR N=2130 TAVI	Mean follow-up: 3.5±2.6 years	2.9 per 1000 person-years	3.4 per 1000 person-years	After propensity score matching, no significant difference in risk of IE after SAVR vs TAVI (HR 1.67, 95% CI 0.61 to 4.59)
Kolte *et al* 2018[13]	Total 95 383 patients identified from the United States Nationwide Readmissions Databases 2013–2014 N=66 077 SAVR N=29 306 TAVI	Median follow-up: SAVR 183 (IQR 91 to 275) days TAVI 153 (IQR 91 to 244) days	25 (95% CI 23 to 29) per 1000 person-years	17 (95% CI 15 to 19) per 1000 person-years	After propensity score matching, no significant difference in the incidence of TAVI-IE and SAVR-IE (17 [95% CI 14 to 20] vs 19 [95% CI 16 to 22] per 1000 person-years, p = 0.29)

CPH, Cox proportional hazards; IE, infective endocarditis; RCT, randomised controlled trial; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

that the risk of IE post-TAVI might be less than for SAVR because of the lack of an open sternotomy wound and reduced need for invasive monitoring following the procedure.

Risk factors for IE after aortic valve replacement

Several risk factors for IE were identified across the entire cohort undergoing aortic valve replacement, including younger age, male sex, atrial fibrillation, dialysis and increased logistic Euroscore. Male sex has previously been reported as a risk factor for prosthetic valve IE after both SAVR and TAVI.[6 19 20] The underlying mechanism is unclear and may be driven by differences in the burden or frequency of bacteraemia, immune response or aortic anatomy.[21] Patients on dialysis were at markedly increased risk of IE (likely due to bacteraemia arising from indwelling lines or dialysis) and represent a key group in whom novel preventative strategies should be targeted.[22]

Specific risk factors for IE after SAVR and TAVI

In patients undergoing SAVR, elevated body mass index was a specific risk factor for IE. Obesity is a well-established risk factor for sternal wound infection after cardiac surgery, and this may explain the increased risk of IE in this subset.[20] We did not observe an association between the type of surgical valve implanted and future IE, in contrast to a prior observational study that suggested increased risk associated with bioprosthetic valves (in comparison with mechanical valves).[19] Unexpectedly, we found that concomitant CABG at the time of SAVR was associated with reduced risk of future IE, a finding which requires further validation.

In patients undergoing TAVI, elevated post-deployment gradient was associated with increased risk of IE. Consistent with these findings, an elevated post-deployment gradient (>15 mmHg) has been identified as a risk factor for IE following transcatheter pulmonary valve implantation.[23] Elevated transvalvular gradients may lead to turbulent flow and endothelial damage, which then acts as a nidus for vegetation formation.[24] Indeed, there may be a role for aggressive post-dilatation to minimise the residual transvalvular gradient. Mechanically expandable valves were also associated with increased risk in our series. Previously, self-expanding valves have also been identified as a risk factor for TAVI-IE, and further studies of the risk associated with different valve designs are required to resolve this discordance.[5] Current expert consensus for prevention of TAVI-IE focuses on antibiotic prophylaxis at the time of implantation, careful patient preparation and sterile implant technique.[25]

Limitations

We used hospital discharge coding data to identify IE cases and there is a possibility that our incidence estimates are underestimates. Reported estimates for coding accuracy for IE vary, with a range for sensitivity of 56%–79% and specificity of 94%–100%.[26 27] In our population, coding was performed independently by trained and accredited personnel. Despite our efforts to mitigate against this, it is possible that some cases of SAVR undertaken as *treatment* for native aortic valve IE may have been miscoded as SAVR-IE. For both cohorts, there are missing data for some variables (as indicated), which we have assumed is missing completely at random. For multivariable modelling, we cannot exclude the possibility of residual confounding accounting for our observations.

Given the very substantial differences in comorbidities and risk scores of the populations undergoing TAVI 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 for interpretation. Although the median follow-up time for the SAVR cohort was longer than for TAVI, the risk of IE appeared to be early after valve intervention, and we do not believe that this affected the difference in (adjusted) incidence rate.

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CONCLUSIONS

IE is a rare adverse outcome following aortic valve replacement which may be slightly less common after TAVI than after SAVR. Key risk factors for IE in patients undergoing aortic valve replacement include younger age, male sex, atrial fibrillation and dialysis. Further research is required to translate insights into this condition into novel preventative strategies.

Key messages

What is already known on this subject?

- Prosthetic valve infective endocarditis (IE) is a potentially life-threatening complication of aortic valve replacement. The relative incidence of IE after SAVR and TAVI, and risk factors for developing prosthetic valve IE, are poorly defined.

What might this study add?

- Prosthetic valve IE was rare, affecting approximately 2% of patients 5 years following aortic valve replacement. The incidence of IE in our population was slightly lower in patients undergoing TAVI compared with SAVR. Risk factors for IE across the study cohort included younger age, male sex, atrial fibrillation and dialysis. In patients undergoing SAVR, elevated body mass index (>30 kg/m^2) and higher logistic Euroscore were also identified as risk factors for IE. In patients undergoing TAVI, implantation of a mechanically expandable valve and an elevated post-implantation peak aortic gradient were specific risk factors for subsequent IE.

How might this impact on clinical practice?

- All patients undergoing aortic valve replacement should be educated about the risk of IE, and these efforts should be amplified in at-risk groups. Further research is required to understand the mechanisms by which IE occurs and translate these insights into novel preventative strategies.

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Correction notice This article has been corrected since it was first published. The total number of SAVR cases in Figure 1 and 2 has been corrected to 91962, as per the main text.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and received Ethical Approval from the London Bromley Research Ethics Committee (reference 16/LO/0275) and the United Kingdom confidentiality advisory group (reference 17CAG0001). These data were acquired retrospectively. Given the high mortality associated with infective endocarditis, we applied to the UK Confidentiality Advisory Group to use anonymised data without consent as it was felt to be not practical to request individual patient consent when a large proportion of patients would already be deceased. This permission was granted after review of the research protocol.

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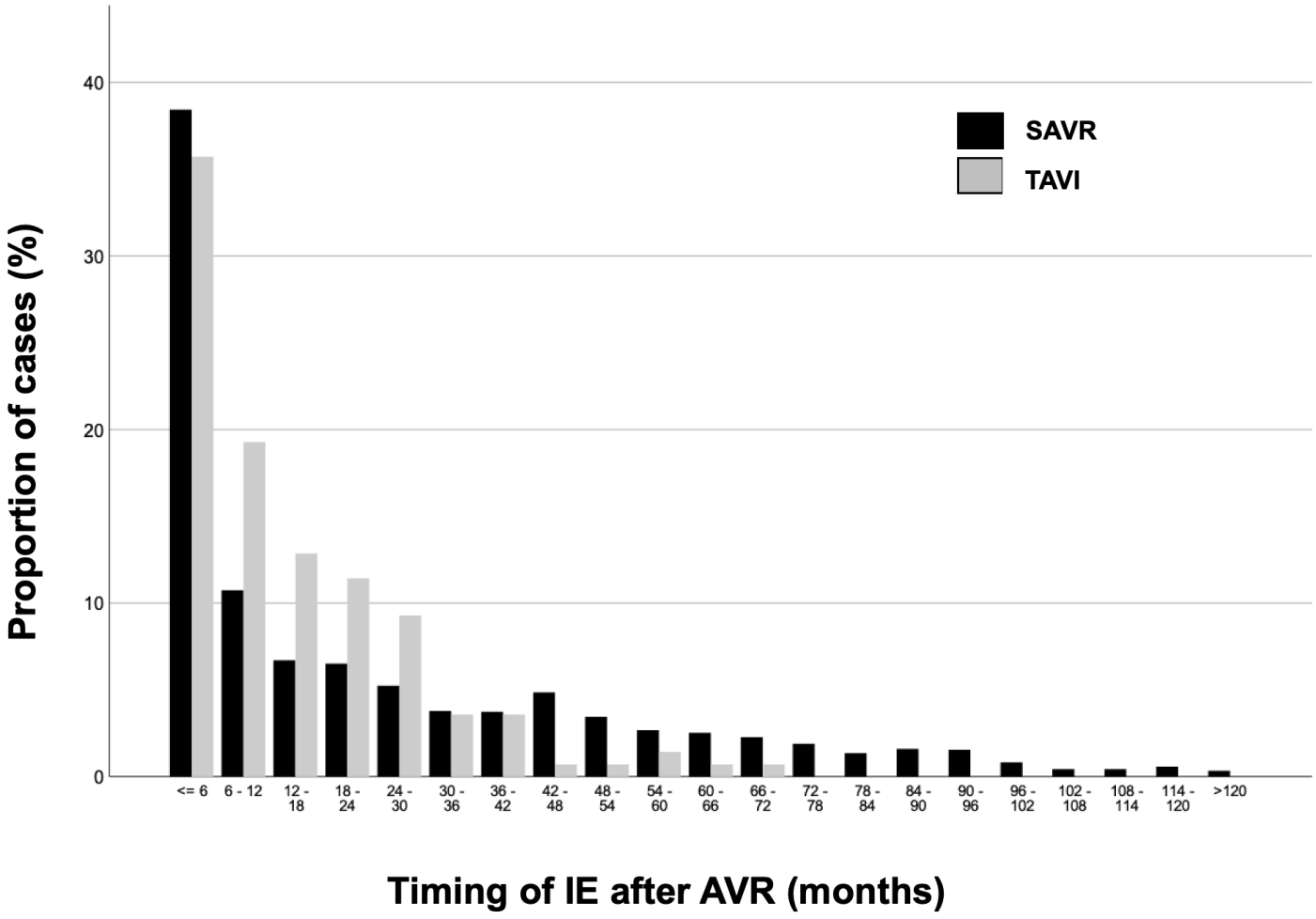
SUPPLEMENTARY TABLE 1: Comparison of baseline TAVI and SAVR populations

		TAVI (n=14195)	SAVR (n=91962)	p-value
Age, median [IQR], y		83.0 [77.0-86.0]	72.0 [63.9-78.1]	<0.001
	NK	128 (0.9%)	0 (0%)	
Sex, n (%)	Male	7595 (53.5%)	58718 (63.9%)	<0.001
	Female	6318 (44.5%)	33239 (36.1%)	
	NK	282 (0.2%)	5 (0%)	
BMI, n (%)	<30	9796 (69.0%)	59714 (63.8%)	<0.001
	>/=30	3554 (25.0%)	29548 (32.1%)	
	NK	845 (6.0%)	3700 (4.0%)	
DM, n (%)	No	10594 (74.6%)	74401 (80.9%)	<0.04
	Yes	3240 (22.8%)	13698 (14.8%)	
	NK	357 (2.5%)	3863 (4.2%)	
Creatinine, µmol/L, [IQR]		97.0 [78.0-123.0]	86.0[73.0-103.0]	<0.001
	NK	567 (4.4%)	36820 (40.0%)	
On dialysis, n (%)	Yes	158 (1.1%)	242 (0.26%)	<0.001
	No	9857 (69.4%)	54900 (59.7%)	
	NK	4180 (29.4%)	61507 (45.9%)	
Previous PCI, n (%)	Yes	2739 (19.3%)	84444 (91.8%)	<0.001
	No	11027 (77.7%)	4929 (5.4%)	
	NK	429 (3.0%)	2589 (2.8%)	
Smoking, n (%)	Yes	409 (2.9%)	84174 (91.5%)	<0.001
	No	6594 (46.5 %)	7068 (7.7%)	
	NK	7192 (50.7%)	720 (0.7%)	
Pulmonary disease, n (%)	Yes	3726 (26.2%)	14302 (15.5%)	<0.001
	No	9975 (70.3%)	77204 (40.0%)	
	NK	494 (3.4%)	456 (0.5%)	
History of AF, n (%)	Yes	3480 (24.5%)	11809 (12.8%)	<0.001
	No	9882 (69.6%)	74338 (80.8%)	
	NK	834 (5.9%)	6923 (5.2%)	

Previous cardiac surgery, n (%)	Yes	3593 (25.3%)	5815 (6.3%)	<0.001
	No	10453 (73.6%)	80029(87.0%)	
	NK	150 (1.1%)	8222 (8.9%)	
PPM, n (%)	Yes	2688 (18.9%)	1624 (1.7%)	<0.001
	No	10781 (75.9%)	84523 (91.9%)	
	NK	726 (5.1%)	5815 (6.3%)	
Logistic Euroscore, [IQR]		16.1 [10.7-25.3]	5.8 [3.3-10.1]	<0.001
	NK	5848 (41.2%)	890 (1.0%)	

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; IQR = interquartile range; NK = not known; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement


Proportion of cases (%)
40
30
20
10
0
SAVR
TAVI
<= 6
6 - 12
12 - 18
18 - 24
24 - 30
30 - 36
36 - 42
42 - 48
48 - 54
54 - 60
60 - 66
66 - 72
72 - 78
78 - 84
84 - 90
90 - 96
96 - 102
102 - 108
108 - 114
114 - 120
>120
Timing of IE after AVR (months)

SUPPLEMENTARY TABLE 2: Interaction terms for predictors of IE after TAVI and SAVR

		HR [95% CI]	p-value for interaction
Age			0.712
	> median	1.45 [1.18-1.77]	
	< median	1.35 [0.93-1.96]	
Sex			0.073
	Male	1.96 [1.43-2.70]	
	Female	1.43 [1.17-2.76]	
BMI > 30			0.528
	Yes	1.75 [1.24-2.47]	
	No	1.62 [1.32-1.99]	
DM			0.999
	Yes	1.60 [1.10-2.32]	
	No	1.63 [1.34-1.98]	
Creatinine			**0.023**
	> median	2.32 [1.84-2.94]	
	< median	1.55 [1.17-2.05]	
On dialysis			0.851
	Yes	42.9 [0.48-52.1]	
	No	0.76 [0.63-0.92]	
Previous PCI			0.517
	Yes	1.74 [1.08-2.81]	
	No	1.58 [1.31-1.91]	
Smoking			0.157
	Yes	4.41 [1.09-17.76]	
	No	1.44 [1.16-1.19]	
Pulmonary disease			0.250
	Yes	1.17 [0.86-1.59]	
	No	1.84 [1.49-2.27]	
History of AF			0.665
	Yes	1.79 [1.26-2.53]	

	No	1.64 [1.33-2.01]	
PPM			0.990
	Yes	1.68 [1.01-2.78]	
	No	1.59 [1.31-1.93]	
Impaired LV function			0.542
	Yes	1.61 [1.29-2.01]	
	No	1.90 [1.43-2.63]	
Logistic Euroscore			0.154
	> median	1.33 [0.553-3.21]	
	< median	2.85 [2.16-2.76]	
Urgency			**<0.001**
	Non-urgent	1.22 [1.02-1.47]	
	Urgent	5.17 [2.77-9.65]	

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; LV = left ventricular; PCI = percutaneous coronary intervention; PPM = permanent pacemaker, TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement

SUPPLEMENTARY TABLE 1: Comparison of baseline TAVI and SAVR populations

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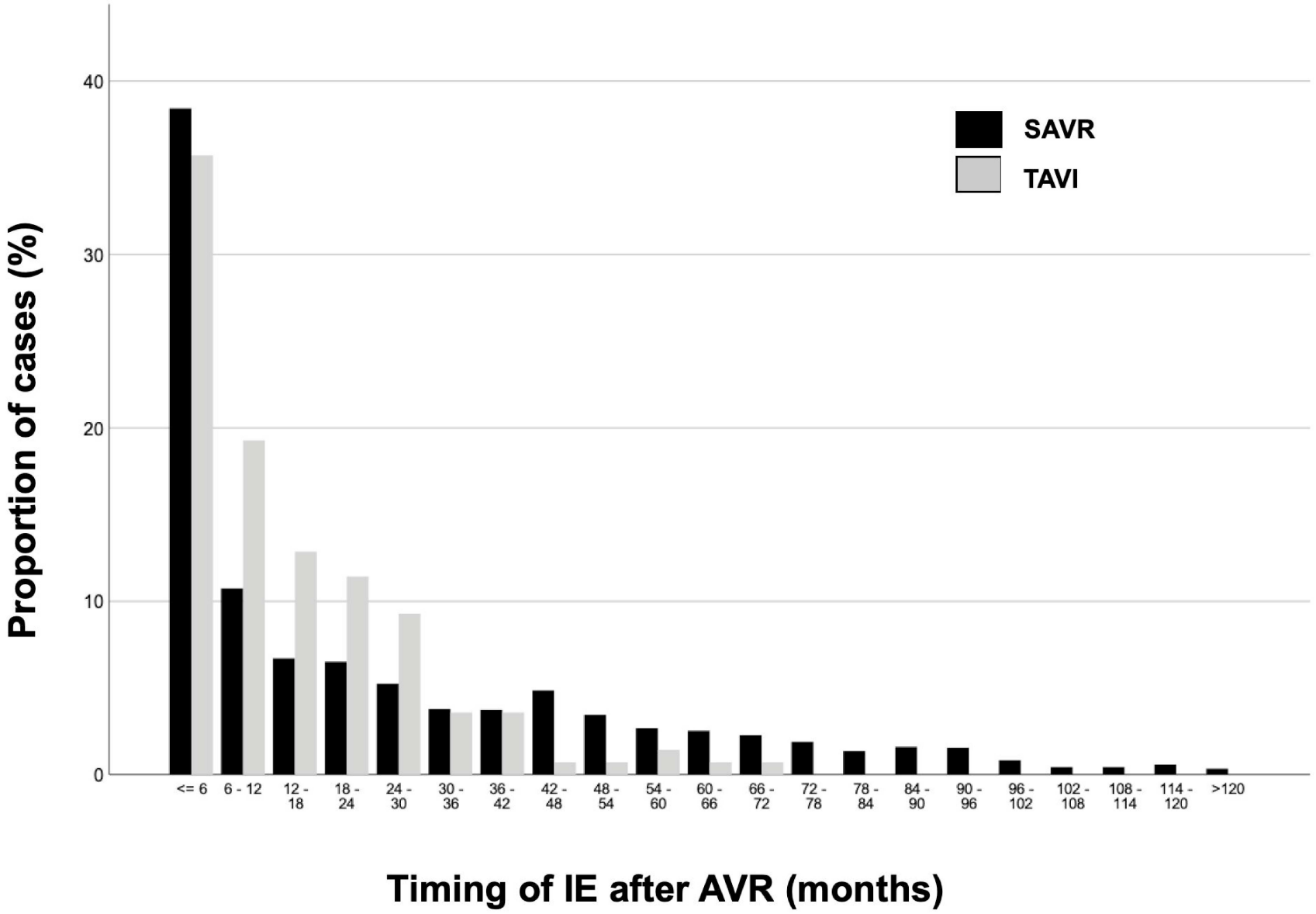
BMI, n (%)	<30	9796 (69.0%)	59714 (63.8%)	<0.001
	>/=30	3554 (25.0%)	29548 (32.1%)	
	NK	845 (6.0%)	3700 (4.0%)	
DM, n (%)	No	10594 (74.6%)	74401 (80.9%)	<0.04
	Yes	3240 (22.8%)	13698 (14.8%)	
	NK	357 (2.5%)	3863 (4.2%)	
Creatinine, μmol/L, [IQR]		97.0 [78.0-123.0]	86.0[73.0-103.0]	<0.001
	NK	567 (4.4%)	36820 (40.0%)	
On dialysis, n (%)	Yes	158 (1.1%)	242 (0.26%)	<0.001
	No	9857 (69.4%)	54900 (59.7%)	
	NK	4180 (29.4%)	61507 (45.9%)	
Previous PCI, n (%)	Yes	2739 (19.3%)	84444 (91.8%)	<0.001
	No	11027 (77.7%)	4929 (5.4%)	
	NK	429 (3.0%)	2589 (2.8%)	
Smoking, n (%)	Yes	409 (2.9%)	84174 (91.5%)	<0.001
	No	6594 (46.5 %)	7068 (7.7%)	
	NK	7192 (50.7%)	720 (0.7%)	
Pulmonary disease, n (%)	Yes	3726 (26.2%)	14302 (15.5%)	<0.001
	No	9975 (70.3%)	77204 (40.0%)	
	NK	494 (3.4%)	456 (0.5%)	
History of AF, n (%)	Yes	3480 (24.5%)	11809 (12.8%)	<0.001
	No	9882 (69.6%)	74338 (80.8%)	
	NK	834 (5.9%)	6923 (5.2%)	

Previous cardiac surgery, n (%)	Yes	3593 (25.3%)	5815 (6.3%)	<0.001
	No	10453 (73.6%)	80029(87.0%)	
	NK	150 (1.1%)	8222 (8.9%)	
PPM, n (%)	Yes	2688 (18.9%)	1624 (1.7%)	<0.001
	No	10781 (75.9%)	84523 (91.9%)	
	NK	726 (5.1%)	5815 (6.3%)	
Logistic Euroscore, [IQR]		16.1 [10.7-25.3]	5.8 [3.3-10.1]	<0.001
	NK	5848 (41.2%)	890 (1.0%)	

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; IQR = interquartile range; NK = not known; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement


Proportion of cases (%)
40
30
20
10
0
SAVR
TAVI
<= 6
6 - 12
12 - 18
18 - 24
24 - 30
30 - 36
36 - 42
42 - 48
48 - 54
54 - 60
60 - 66
66 - 72
72 - 78
78 - 84
84 - 90
90 - 96
96 - 102
102 - 108
108 - 114
114 - 120
>120
Timing of IE after AVR (months)

SUPPLEMENTARY TABLE 2: Interaction terms for predictors of IE after TAVI and SAVR

		HR [95% CI]	p-value for interaction
Age			0.712
	> median	1.45 [1.18-1.77]	
	< median	1.35 [0.93-1.96]	
Sex			0.073
	Male	1.96 [1.43-2.70]	
	Female	1.43 [1.17-2.76]	
BMI > 30			0.528
	Yes	1.75 [1.24-2.47]	
	No	1.62 [1.32-1.99]	
DM			0.999
	Yes	1.60 [1.10-2.32]	
	No	1.63 [1.34-1.98]	
Creatinine			**0.023**
	> median	2.32 [1.84-2.94]	
	< median	1.55 [1.17-2.05]	
On dialysis			0.851
	Yes	42.9 [0.48-52.1]	
	No	0.76 [0.63-0.92]	
Previous PCI			0.517
	Yes	1.74 [1.08-2.81]	
	No	1.58 [1.31-1.91]	
Smoking			0.157
	Yes	4.41 [1.09-17.76]	
	No	1.44 [1.16-1.19]	
Pulmonary disease			0.250
	Yes	1.17 [0.86-1.59]	
	No	1.84 [1.49-2.27]	
History of AF			0.665
	Yes	1.79 [1.26-2.53]	

	No	1.64 [1.33-2.01]	
PPM			0.990
	Yes	1.68 [1.01-2.78]	
	No	1.59 [1.31-1.93]	
Impaired LV function			0.542
	Yes	1.61 [1.29-2.01]	
	No	1.90 [1.43-2.63]	
Logistic Euroscore			0.154
	> median	1.33 [0.553-3.21]	
	< median	2.85 [2.16-2.76]	
Urgency			**<0.001**
	Non-urgent	1.22 [1.02-1.47]	
	Urgent	5.17 [2.77-9.65]	

AF = atrial fibrillation; BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; LV = left ventricular; PCI = percutaneous coronary intervention; PPM = permanent pacemaker, TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement