Pre-implantation Balloon Aortic Valvuloplasty and Clinical Outcomes Following Transcatheter Aortic Valve Implantation: A Propensity Score Analysis of the UK Registry

Running title: *Martin et al. BAV and clinical outcomes after TAVI*

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Abstract

Background

Aortic valve pre-dilation with Balloon Aortic Valvuloplasty (BAV) is recommended prior to Transcatheter Aortic Valve Implantation (TAVI), despite limited data around the requirement of this pre-procedural step and the potential risks of embolisation. This study aimed to investigate the trends in practice and associations of BAV on short-term outcomes in the UK TAVI registry.

Methods and Results

Eleven clinical endpoints were investigated including 30-day mortality, myocardial infarction, aortic regurgitation, valve dysfunction and composite early safety. All endpoints were defined as per the VARC-2 definitions. Odd ratios of each endpoint were estimated using logistic regression, with data analysed in balloon-expandable and self-expandable valve subgroups. Propensity scores were calculated using patient demographics and procedural variables, which were included in the models of each endpoint to adjust for measured confounding.

Between 2007 and 2014, 5887 patients met the study inclusion criteria, 1421 (24.1%) of whom had no BAV before TAVI valve deployment. We observed heterogeneity in the use of BAV nationally, both temporally and by centre experience; rates of BAV in pre-TAVI work-up varied between 30% and 97% across TAVI centres. All endpoints were similar between treatment groups in SAPIEN valve patients. After correction for multiple testing, none of the endpoints in CoreValve patients were significantly different between patients with or without pre-dilation.

Conclusions

Performing TAVI without pre-dilation was not associated with adverse short-term outcomes post procedure, especially when using a balloon-expandable prosthesis. Randomised trials including different valve types are required to provide conclusive evidence regarding the utility of pre-dilation before TAVI.

Keywords

Transcatheter aortic valve implantation - balloon-expandable - self-expandable – balloon valvuloplasty – aortic stenosis

Introduction

Transcatheter aortic valve implantation (TAVI) is an effective treatment option for multi-morbid patients with severe symptomatic aortic stenosis (AS) who are either not suitable for conventional surgical aortic valve replacement or who are deemed high-risk surgical candidates [1–4].

During the TAVI procedure, recommendations have included the use of balloon aortic valvuloplasty (BAV) to pre-dilate the aortic valve before the deployment of the transcatheter valve. Such pre-dilation is intended to aid delivery of the prosthesis across the valve, enhance prosthesis expansion in the aortic annulus, provide information about the aortic annulus size and potentially improve hemodynamic performance during the TAVI procedure [5]. Additionally, BAV during TAVI can be used to evaluate possible coronary occlusion in patients with low coronary height. However, BAV is associated with complications, including stroke, conduction disturbances and severe aortic regurgitation [6,7]. Thus, it is possible that the routine use of BAV in TAVI procedures actually increases procedural risk. Whilst it is routine for many TAVI centres to pre-dilate using BAV, recent preliminary studies have indicated that TAVI without pre-dilation is feasible in both Edwards SAPIEN and Medtronic CoreValve prostheses [8–14]. However, much of the previously published data in this area is derived from small single-centre studies and subject to sampling bias, with little data on utility of BAV and its associated clinical outcomes following TAVI in large multi-centre TAVI registries.

Therefore, this analysis was undertaken in the UK TAVI registry to investigate patterns of BAV use across the UK and its association with short-term clinical outcomes following TAVI.

Methods

UK TAVI Registry

The UK TAVI registry uses a Web-based interface provided by the National Institute of Cardiovascular Outcomes Research to collect data prospectively on every TAVI procedure conducted in the UK [15]. There are currently thirty-four centres running active TAVI programs, with data collection being mandatory [15]. The dataset comprises ninety-five variables, detailing patient demographics, risk factors for intervention, procedural details and adverse outcomes up to the time of hospital discharge. Patient life status is provided by record linkage with the Office for National Statistics for English and Welsh patients. Mortality information for Northern Irish patients and the majority of Scottish patients was unavailable and consequently these patients were removed from the analysis.

This study analysed data from January 2007 to December 2014. The Edwards SAPIEN (Edwards Lifesciences Inc., Irvine, CA, USA) and the Medtronic CoreValve (Medtronic, Minneapolis, MN, USA) prostheses were available to all centres throughout the study period.

Study Design

Endpoints in this study were 30-day mortality and the following events occurring up to hospital discharge: myocardial infarction (MI), stroke, paravalvular leak (PVL) / moderate-severe aortic regurgitation (AR), coronary artery obstruction (CAO), valve dysfunction requiring repeat procedure, permanent pacemaker implantation (PPM) requirement, device migration, kidney injury, major vascular complications (MVC) and composite early safety. All endpoints were defined as given in the VARC-2 definitions [16].

This analysis defined BAV procedures based on when any such procedure was completed relative to the time of TAVI. Specifically, we distinguished the following timings:

(1) BAVs completed prior to the date of TAVI (Prior-TAVI BAV), (2) BAVs completed as part of the TAVI procedure but before valve deployment (During-TAVI BAV) and (3) no BAV prior or during the TAVI procedure (Direct TAVI). Since the aim of this study was to investigate the effect of pre-dilation on TAVI outcomes, the main analysis excluded any patient who had a BAV prior to the date of TAVI; hence, the main analysis compared endpoints across patients with a During-TAVI BAV (but none prior) and Direct TAVI, with the latter group taken as the reference. All patients with missing treatment group identifiers were excluded.

Additionally, to investigate if the timing of the BAV relative to the TAVI procedure was associated with outcomes, we conducted a sensitivity analysis that did not exclude those patients who had a BAV prior to the date of TAVI. Hence, the sensitivity analysis compared outcomes across all four possible treatment groups: (i) Prior-TAVI BAV and During-TAVI BAV; (ii) Prior-TAVI BAV & No During-TAVI BAV; (iii) No Prior-TAVI BAV & During-TAVI BAV; and (iv) No Prior-TAVI BAV & No During-TAVI BAV (Direct TAVI). Here, groups (iii) and (iv) comprised exactly those patients as in the main analysis.

Since the effects of BAV on outcomes after TAVI were potentially dependent on the expansion method of the valve type (balloon-expandable or self-expandable), all analyses were completed in device specific subgroups (SAPIEN vs CoreValve). Patients were excluded only from the valve-subgroup analyses if they were not treated with a SAPIEN or CoreValve prosthesis or if the valve type was unknown.

Statistical Analysis

Continuous data were presented as means and standard deviations with group comparisons done with analysis of variance. Categorical data were presented as counts and percentages with group comparisons done using the chi-squared test.

Every variable with missing data was imputed using multiple imputation [17]. Ten imputed datasets were generated using multiple imputation by chained equations. The imputation model for each variable included the majority of other variables in the UK TAVI registry. Additionally, to avoid underestimation of covariate-outcome associations, all endpoints were used in the imputation models for missing covariates [18]. After such imputation, the imputed outcome values were returned to the original values (i.e. missing), following the so-called multiple imputation, then deletion approach [19]. All patients with missing life-status were excluded from the analysis; patients with other endpoints missing were only excluded from the analysis of that particular endpoint. Analyses were undertaken in each dataset separately, before pooling results according to Rubin's rules [17].

To investigate clinical outcomes across treatment groups, propensity scores (PS) for being in each treatment group were calculated for all patients to control for potential confounders and baseline differences [20,21]. A logistic regression model calculated each patient's PS, given the baseline covariates, which included every variable listed in **Table 1** (except the LES and STS score), in addition to a TAVI centre experience indicator and year of procedure. For the sensitivity analysis, a multinomial logistic regression model was used to calculate each patient's PS for each treatment group, which included exactly the same covariates as for the main analysis. Odds ratios (ORs) for each endpoint across BAV treatment groups were estimated using a logistic regression model that was fitted to each outcome with the treatment group indicator and the PS as covariates. A Bonferroni correction was applied to account for multiple testing.

Patient characteristics that resulted in a higher probability to perform pre-dilation were identified by deriving a logistic regression model with During-TAVI BAV (no prior BAV) as the dependent variable. Predictors associated with the use of pre-dilation were investigated by backwards selection using Akaike information criterion (AIC) in each

imputed dataset, resulting in ten (potentially different) sets of selected predictors. Predictors that were selected in more than 50% of the ten imputed datasets were identified as independent predictors of During-TAVI BAV, following the so-called "majority method" of selecting variables in multiple imputed data [22]. Given the selected predictors, a logistic regression model was fitted in each of the ten imputed datasets with estimated coefficients and standard errors then pooled according to Rubin's rules [17].

R version 3.3.1 [23] was used for all statistical analyses. Graphical plots where made using the ggplot2 package [24] and the mice package was used for the multiple imputation [25].

Results

From January 2007 to December 2014, 7431 patients underwent a TAVI procedure in the UK. The flow of patients through the steps of exclusion criteria is illustrated in **Figure 1**. Specifically, the analysis set for the main analysis comprised of 5887 patients; 1421 patients (24.1%) had no BAV (Direct TAVI) and 4466 patients (75.9%) had a During-TAVI BAV. Together, 3201 patients had a SAPIEN valve, 2467 patients had a CoreValve and the remaining 219 patients were treated with another or unknown valve type. For the sensitivity analysis, which did not exclude prior-to-TAVI BAV patients, the analysis set included exactly those patients in the main analysis in addition to 507 patients who had a Prior & During-TAVI BAV and 197 patients who had a Prior-TAVI BAV but no During-TAVI BAV.

Summary statistics of baseline characteristics for the main analysis are given in **Table 1**. The During-TAVI BAV group had significantly higher mean age and higher proportions of patients with extracardiac arteriopathy, calcification of ascending aorta, NYHA class III or IV, and one or more disease coronary vessels, but significantly smaller proportions of patients with previous cardiac surgery and pulmonary hypertension. Patients in the During-TAVI BAV group had a significantly smaller mean aortic valve area and significantly larger aortic peak gradient than in the Direct TAVI group ($p<0.01$), although the proportion of

patients with impaired Left Ventricular function at the time of the TAVI procedure was similar (p=0.47). The Logistic EuroSCORE (LES) and STS score models were calculated in each multiply imputed dataset using the variables and coefficients previously published [26,27]. Hence, the ranges of the mean and standard deviations across each imputed dataset are given; predicted risk as estimated by both models was significantly different across treatment groups (**Table 1**).

Trends in BAV Practice

Between 2007 and 2014 there was a decreasing trend in the proportion of patients undergoing pre-dilation in the whole cohort (p<0.001) and by access route (p=0.001) (**Figure 2**). A similar pattern of longitudinal behaviour was observed over SAPIEN and CoreValve patients. Additionally, there was heterogeneity in practice amongst centres, with During-TAVI BAV group rates varying from 30% to 97% (**Figure 3**). Interestingly, there was a visual trend of decreased use of BAV for successive increases in centre experience, with the exception of the two very highest volume groups (251-300 and 300+), which represented just seven centres (**Figure 4**). Specifically, when a centre had undertaken between 1 and 50 previous TAVI procedures, rates of During-TAVI BAV were 89%, but this had decreased to 50% when centres had undertaken between 201 and 250 previous TAVIs.

TAVI Outcomes by BAV Treatment Group

Table 2 gives the PS adjusted odds ratios for each outcome in the whole cohort for the main analysis. Before adjusting for multiple testing, patients with a During-TAVI BAV had increased odds of having a permanent pacemaker (OR of 1.30). However, this was not significant after correcting for multiplicity (**Table 2**). There were no other significant differences in other endpoints between the two treatment groups. Similar findings were obtained in the sensitivity analysis of the four-treatment groups (**Table 3**).

When studying patients treated with the balloon-expandable SAPIEN valve, there were no significant differences in any of the endpoints between During-TAVI BAV and Direct TAVI treatment groups (**Table 4**). For the self-expanding CoreValve prosthesis, before multiplicity correction the During-TAVI BAV group had significantly lower odds of valve dysfunction (OR of 0.58) over those undergoing Direct TAVI. However, this finding was not significant after multiplicity correction (**Table 4**). Other endpoints were not significantly different across treatment groups in the CoreValve subgroup. Similar findings for the SAPIEN and CoreValve subgroups were observed in the sensitivity analysis of the four-treatment-group analysis (**Table 5** and **Table 6**).

Predictors of During-TAVI BAV

Variables that were independently associated with the use of pre-dilation are given in **Figure 5**. Odds of undergoing During-TAVI BAV were significantly lower with increasing year of procedure and with increasing number of TAVI procedures for a given centre, which supports the trend analysis after multivariable adjustment. Additionally, female patients with larger aortic valve area, previous cardiac surgery, pulmonary hypertension and non-elective procedures were significantly less likely to undergo a During-TAVI BAV. Conversely, calcification of ascending aorta, NYHA class III or IV and transfemoral access were associated with significantly increased odds of During-TAVI BAV.

Discussion

This analysis of 5887 UK TAVI procedures has shown heterogeneity in the use of BAV nationally. Importantly, outcomes were not significantly different between patients who had a Direct TAVI and those who only had a BAV as part of the TAVI procedure. Notably, there were no significant differences in all outcomes across any of the treatment groups in SAPIEN valve patients. Similarly, after correction for multiple testing, there were no

significant differences between those with and without BAV in patients treated with a CoreValve prosthesis. These findings support those from a recent meta-analysis, which showed similar outcomes after TAVI both with and without pre-dilation [13].

Although using BAV pre-TAVI may help to prepare the calcified aortic valve, standalone BAV procedures are associated with several complications [6,28]; hence, removing the pre-dilation step may simplify the TAVI procedure. This study highlighted that the proportion of TAVI patients in the UK having a BAV in pre-TAVI work-up is decreasing through time. Despite pre-dilation before TAVI valve deployment being the most common procedure throughout the majority of UK TAVI centres, several centres conducted relatively high proportions of Direct TAVI procedures. The reasons behind these changes in procedure are unclear from the current work, but certainly translate the progress along the learning curve that leads to more confidence with direct implantation.

BAV Outcomes in SAPIEN Valve patients

An important finding of the current study was that there were no significant differences over any of the clinical outcomes between treatment groups in the SAPIEN valve patients. These results are consistent with previous studies [8,9,12,14,29]. A study that compared 50 transapical access patients with BAV to 50 transapical access patients without BAV, found no significant differences in any of the endpoints defined in the VARC-2 definitions [8]; this finding was later supported with studies on transfemoral access SAPIEN-TAVI patients [9]. In contrast, previous work has suggested that SAPIEN-TAVI without BAV is associated with higher volume of cerebral ischemic lesions [30]. In the current study, differences between stroke outcomes over the two treatment groups were not significant. Once published, findings from a planned multicentre two-armed observational trial (EASE-IT) comparing SAPIEN TAVI patients with or without pre-dilation, will provide further insights [31]. The present study suggests that SAPIEN TAVI procedures can feasibly be conducted without routine BAV,

without increased risk in adverse outcomes. However, a degree of selection on a patient level is advocated, likely based on the extent of calcification and movement of leaflets, but also based on if a patient has impaired LV function where one might want to minimise pacing time during TAVI.

BAV Outcomes in CoreValve patients

After correction for multiple testing, there were no significant differences with and without pre-dilation in CoreValve patients. When testing many endpoints, one would expect to find positive results by chance simply due to the way hypothesis testing is conducted [32]. Nonetheless, the feasibility of conducting TAVI without BAV in CoreValve patients was first proposed in a pilot study of 60 patients [11]. Subsequent studies have shown that clinical outcomes are similar between BAV treatment groups in CoreValve patients [10,33,34]. Theoretically, conducting TAVI without BAV in self-expanding valves could potentially lead to worse outcomes. For example, without BAV, self-expanding valves may not achieve as good expansion and may therefore fail to reach optimal deployment dimensions, particularly in heavily calcified aortic annuli. While the current study highlights the potential to remove the pre-dilation step in CoreValve TAVI procedures with regard to clinical outcomes, further work in this subgroup of patients will be required. For example, it is possible that patients undergoing CoreValve TAVI without prior BAV will require post-dilatation more frequently to correct for stent under expansion and/or paravalvular leakage. The majority of patients in the current study did not have data on post-dilation requirement and so this endpoint could not be analysed.

Timing of BAV Relative to TAVI

We hypothesised a priori that the timing and indication for performing BAV could be related to the impact on subsequent clinical outcomes. Consequently, the sensitivity analysis

included those patients who had a BAV as a bridge to TAVI (i.e. a BAV completed prior to the date of the TAVI procedure), who represent a specific complex group of patients. All outcomes were similar between those who had a BAV prior to the date of TAVI (with or without subsequent BAV during TAVI) and those undergoing Direct TAVI. However, although we were able to distinguish the patients who had a BAV as a bridge to TAVI, the UK registry does not capture the reasons a BAV was conducted. Hence, this study could not investigate the full impact of BAVs conducted prior-to-TAVI. Prior-to-TAVI dilation is often conducted when a patient has presented with severe AS or when there are questions regarding the clinical benefit of a TAVI procedure. Therefore, one could argue that TAVI might not be feasible in such cases, without the period of convalescence after the preparatory BAV. Further work in such patients is recommended, as there is a paucity of data for this specific cohort of patients.

Limitations

One limitation of the current work is that outcomes associated with the decision to use BAV were studied in this retrospective study. Such a design may introduce significant selection biases since the UK TAVI registry does not capture the reasons why or how each BAV was conducted. As such, any reported relationships cannot be interpreted as causal and they may relate to unmeasured confounders or selection bias. The inclusion of most patient demographic, procedural information and TAVI centre experience in the PS models should mitigate the effects of this as much as possible. Likewise, patients who undergo a BAV are generally more severe cases with complex anatomy and would hence be expected to have poorer outcomes over those who do not undergo BAV, the use of PS in the correct work aims to correct for such confounding by indication. Finally, the absence of information regarding hemodynamic performance, valve failure rates and echocardiographic outcomes means that

such outcomes were unable to be analysed. Similarly, we were unable to investigate technical difficulties, which have previously been indicated in Direct TAVI patients [14].

Conclusion

This large-scale study highlights that a no-BAV (Direct TAVI) approach has similar clinical outcomes to the current practice of using BAV to pre-dilate the diseased valve, especially when using a balloon-expandable prosthesis. Although this analysis provides evidence that omitting the BAV step is feasible, this warrants prospective randomised studies to define further the utility of BAV.

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Conflict of Interest Disclosures

None.

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Figure Legends

Figure 1: Flowchart illustrating the exclusion criteria applied to the UK TAVI registry.

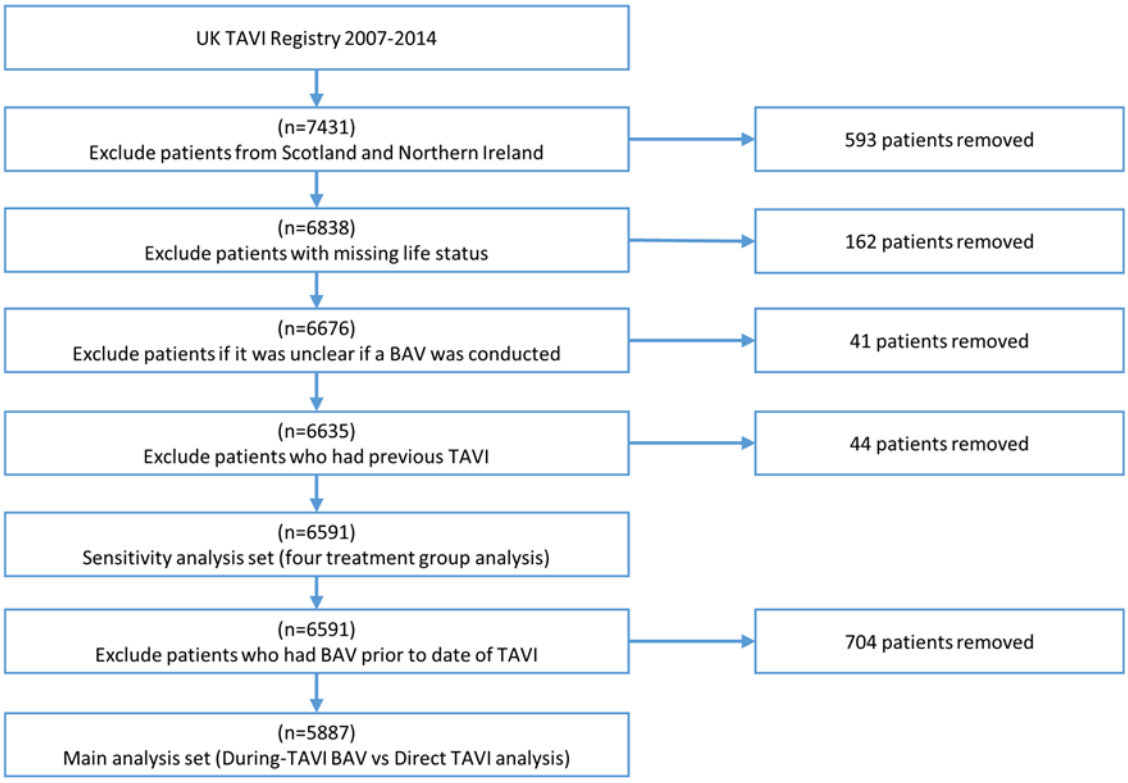


Figure 2: The longitudinal changes in the proportion of TAVI patients having During-TAVI BAV (no BAV prior to TAVI) and Direct TAVI in the whole cohort and by access route.

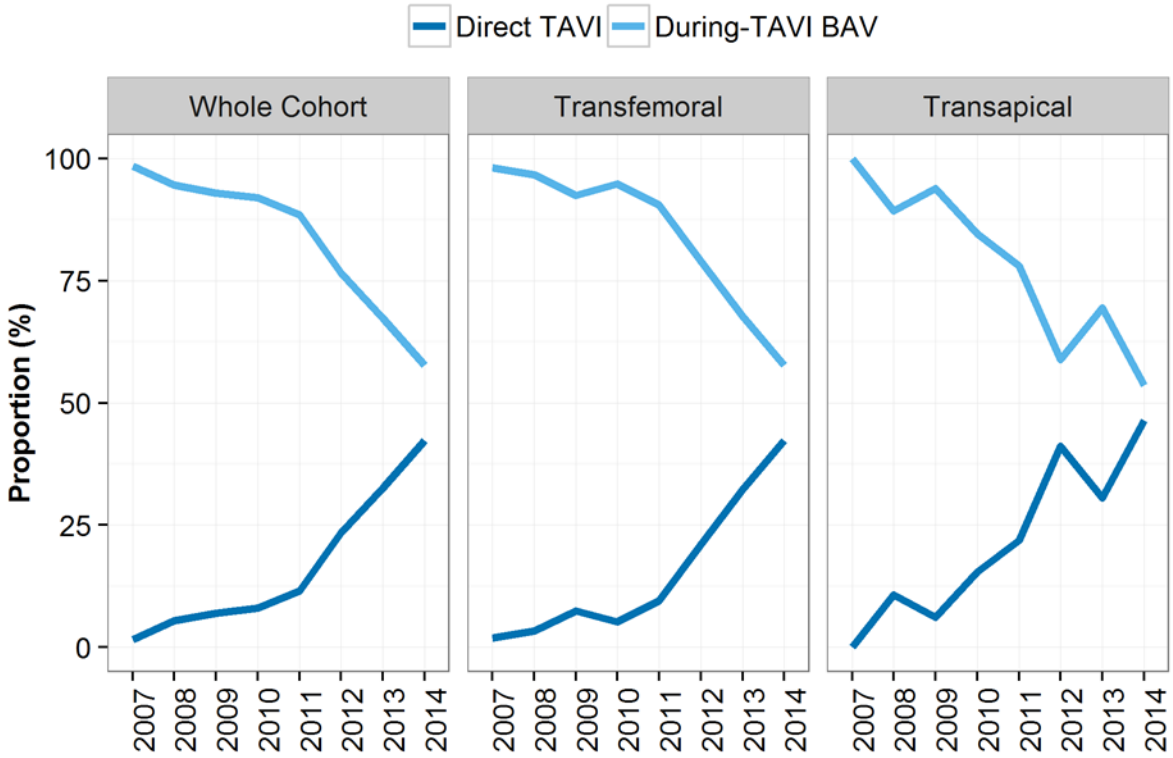


Figure 3: The proportion of patients having During-TAVI BAV (no BAV prior to TAVI) and Direct TAVI over the 32 centres running active TAVI programs in the England and Wales by 2014. The centres on the x-axis have been sorted based on the total number of TAVI procedures each has conducted.

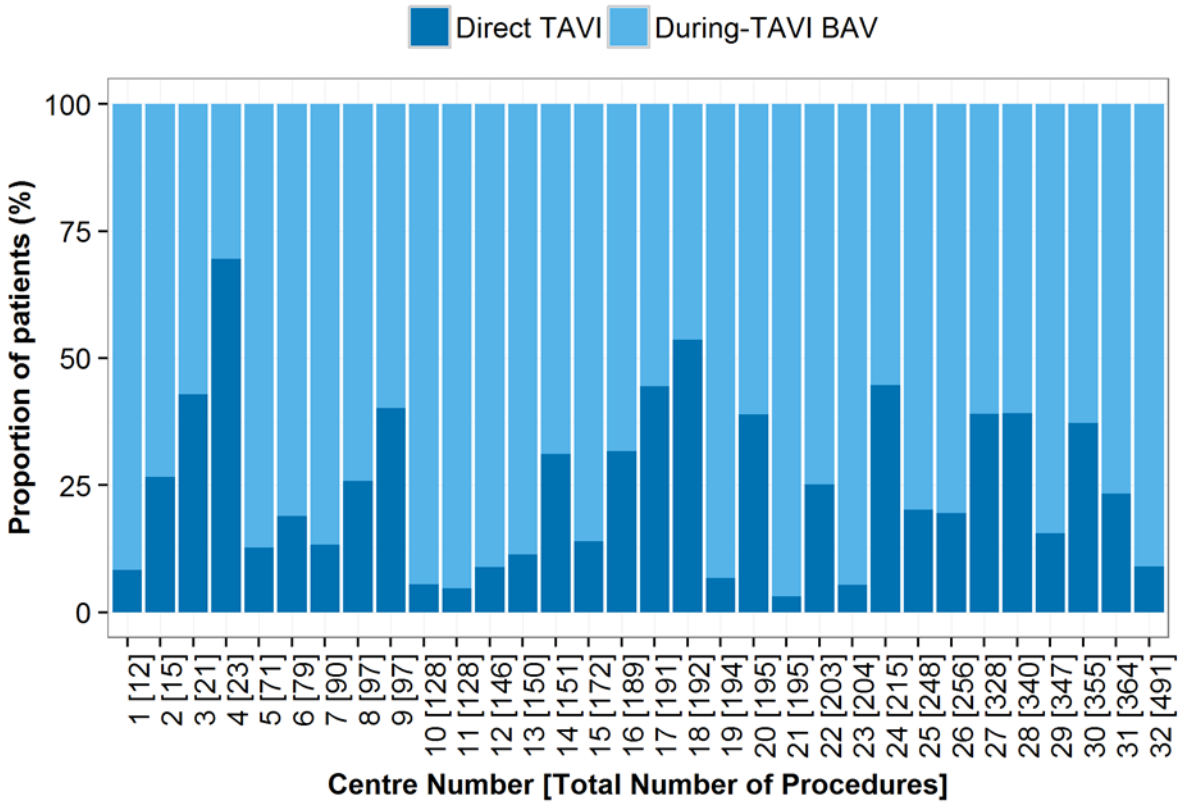


Figure 4: The proportion of patients in each treatment group by centre experience. The x-axis shows the number of TAVI procedures conducted within a centre prior to each patient within that centre.

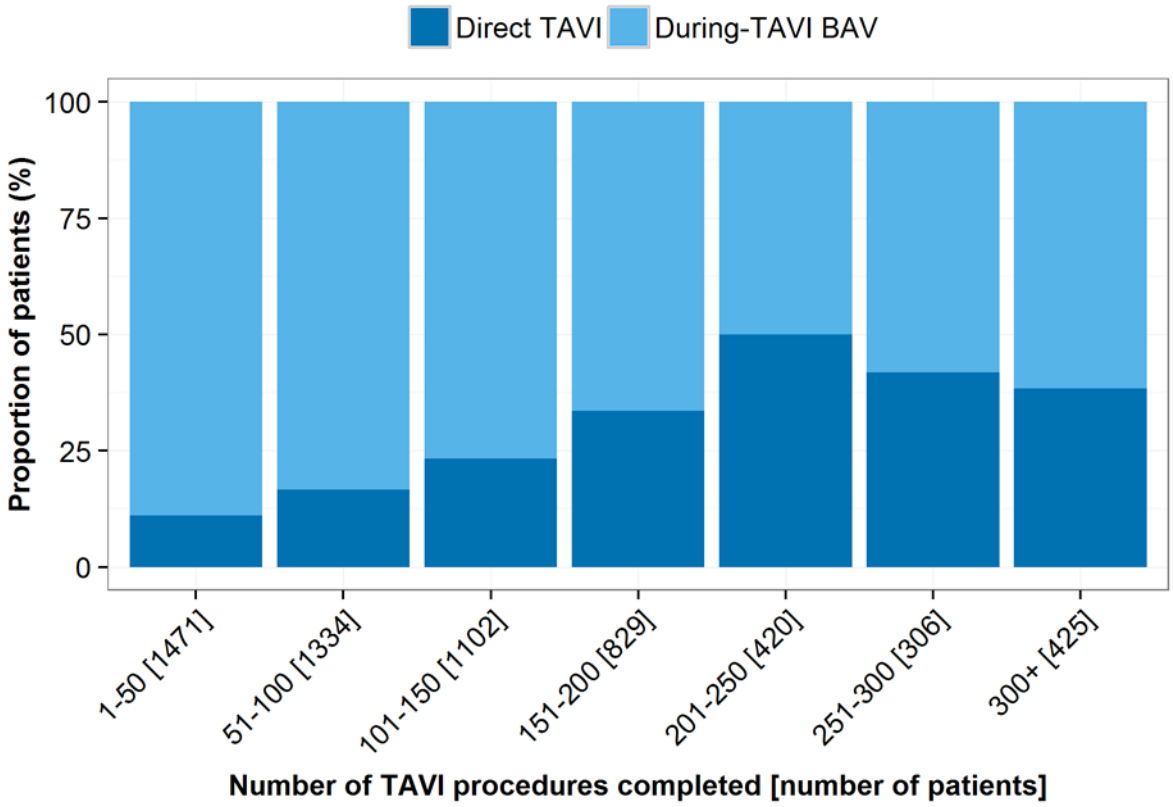
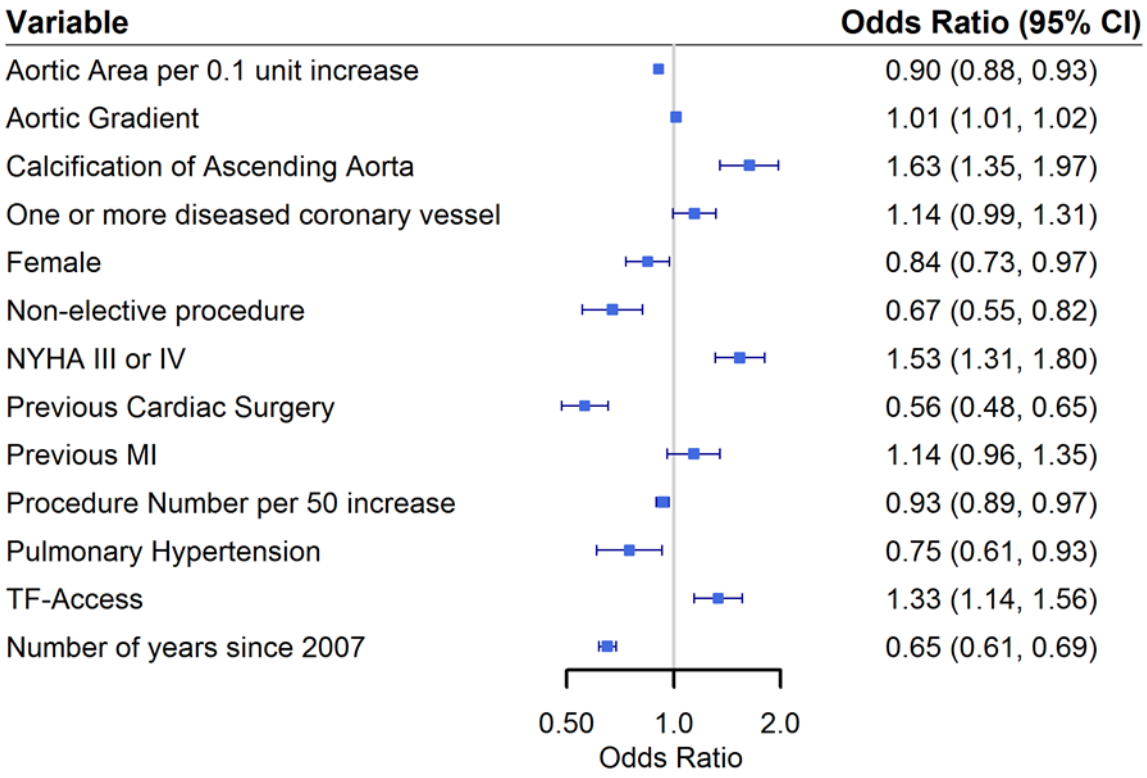


Figure 5: Odds ratios of variables that were identified as independent predictors of a patient being in the During-TAVI BAV group.



Tables

Table 1. Baseline characteristics across the treatment groups in the main analysis that excluded BAVs conducted prior-to-TAVI.

Variable	Whole Cohort (n=5887)	During-TAVI BAV (n=4466)	Direct TAVI (n=1421)	p-value	Missing (%)
Age, mean (SD)	81.3 (7.5)	81.5 (7.2)	80.5 (8.2)	<0.001	0 (0.00)
Female, n (%)	2755 (46.8)	2125 (47.6)	630 (44.3)	0.03	21 (0.36)
Diabetic, n (%)	1351 (22.9)	1019 (22.8)	332 (23.4)	0.70	6 (0.10)
Smoker, n (%)	3051 (51.8)	2351 (52.6)	700 (49.3)	0.10	201 (3.4)
Creatinine, mean (SD)	113.7 (64.9)	112.8 (64.0)	116.3 (67.5)	0.08	44 (0.75)
Renal Failure *, n (%)	351 (6.0)	250 (5.6)	101 (7.1)	0.05	72 (1.2)
Previous MI, n (%)	1246 (21.2)	936 (21.0)	310 (21.8)	0.50	6 (0.10)
Pulmonary Disease, n (%)	1648 (28.0)	1262 (28.3)	386 (27.2)	0.38	51 (0.9)
Neurological Disease, n (%)	1011 (17.2)	790 (17.7)	221 (15.6)	0.07	6 (0.10)
Extracardiac Arteriopathy, n (%)	1390 (23.6)	1085 (24.3)	305 (21.5)	0.02	51 (0.87)
Calcification of Ascending Aorta, %	1106 (18.8)	923 (20.7)	183 (12.9)	<0.001	44 (0.75)

(n)					
Atrial Fibrillation, n (%)	1434 (24.4)	1071 (24.0)	363 (25.5)	0.28	68 (1.2)
Previous Cardiac Surgery, n (%)	1884 (32.0)	1299 (29.1)	585 (41.2)	<0.001	6 (0.10)
Previous PCI, n (%)	1141 (19.4)	877 (19.6)	264 (18.6)	0.40	6 (0.10)
Height, mean (SD)	1.65 (0.10)	1.64 (0.10)	1.65 (0.10)	0.01	110 (1.9)
Weight, mean (SD)	74.1 (16.4)	73.9 (16.4)	74.8 (16.4)	0.06	87 (1.5)
CCS Class 4, n (%)	70 (1.2)	53 (1.2)	17 (1.2)	0.99	10 (0.17)
NYHA ≥ III, n (%)	4708 (80.0)	3642 (81.5)	1066 (75.0)	<0.001	15 (0.25)
Pulmonary Hypertension, n (%)	677 (11.5)	499 (11.2)	178 (12.5)	0.001	1652 (28.1)
Aortic Valve Area, mean (SD)	0.68 (0.22)	0.66 (0.20)	0.74 (0.28)	<0.001	325 (5.5)
Aortic Valve Peak Gradient, mean (SD)	75.6 (25.9)	78.4 (25.4)	66.3 (25.5)	<0.001	222 (3.8)
LVEF < 50%, n (%)	2160 (36.7)	1628 (36.5)	532 (37.4)	0.47	28 (0.48)
One or more diseased vessels, n (%)	2507 (42.6)	1952 (43.7)	555 (39.1)	0.001	71 (1.2)
Left Main Stem Disease, n (%)	271 (4.6)	215 (4.8)	56 (3.9)	0.22	102 (1.7)
Non-elective	702 (11.9)	478 (10.7)	224 (15.8)	<0.001	2 (0.03)

Procedure, n (%)					
LES, mean (SD) †	21.4 – 21.5 (13.7-13.9)	21.4-21.5 ± 13.4-13.5	22.8-23.2 ± 14.8-15.1	<0.001	NA
STS Score, mean (SD) †	4.9-5.0 (4.0-4.1)	5.0-5.0 ± 3.7-3.8	5.1-5.2 ± 4.6-4.7	0.01	NA
Access Site					5 (0.08)
Transfemoral, n (%)	4385 (74.5)	3326 (74.5)	1059 (74.5)	0.92	
Transapical, n (%)	952 (16.2)	709 (15.9)	243 (17.1)	0.28	
Subclavian, n (%)	223 (3.8)	194 (4.3)	29 (2.0)	<0.001	
Other, n (%)	322 (5.5)	235 (5.3)	87 (6.1)	0.23	

** Defined as creatinine >200µmol/l or dialysis for renal failure. † The Logistic EuroSCORE and STS models were calculated using the imputed data and so ranges are given for these variables for the summary measures across the ten multiply imputed datasets; variables that were included in either model but were not recorded in the UK TAVI registry were assumed risk factor absent. LES: Logistic EuroSCORE, LVEF: Left Ventricular Ejection Fraction, MI: Myocardial Infarction, NYHA: New York Heart Association, PCI: Percutaneous coronary intervention, STS: Society of Thoracic Surgeons Score for Prediction of Mortality*

Table 2. Crude event rates and PS regression adjusted odds ratios (OR) for each of the considered outcomes in the whole cohort for the main analysis that excluded BAVs conducted prior-to-TAVI.

Outcome	**During-TAVI BAV (n=4466)**	**Direct TAVI (n=1421)**	**PS adjusted OR (95% CI) without Bonferroni correction**	**PS adjusted OR (95% CI) with Bonferroni correction**
30-day mortality	239/4466 (5.4%)	63/1421 (4.4%)	1.04 (0.76, 1.42)	1.04 (0.63, 1.72)
MI	36/4442 (0.81%)	8/1411 (0.57%)	1.03 (0.45, 2.35)	1.03 (0.27, 3.93)
Stroke	132/4445 (3.0%)	35/1409 (2.5%)	0.91 (0.60, 1.37)	0.91 (0.47, 1.77)
Moderate/ Severe AR/PVL	432/4043 (10.7%)	79/1314 (6.0%)	1.30 (0.99, 1.69)	1.30 (0.84, 2.00)
CAO	35/4441 (0.79%)	12/1410 (0.85%)	0.80 (0.39, 1.65)	0.80 (0.25, 2.59)
Valve Dysfunction	136/4426 (3.1%)	40/1407 (2.8%)	0.78 (0.53, 1.15)	0.78 (0.41, 1.47)
Pacemaker implantation	520/4439 (11.7%)	130/1405 (9.3%)	**1.30 (1.04, 1.62)**	1.30 (0.91, 1.86)
Device Migration	72/4437 (1.6%)	24/1402 (1.7%)	1.21 (0.72, 2.03)	1.21 (0.52, 2.80)

Haemofiltration/ Dialysis	178/4426 (4.0%)	70/1405 (5.0%)	0.89 (0.65, 1.22)	0.89 (0.53, 1.48)
MVC	177/4431 (4.0%)	56/1407 (4.0%)	0.84 (0.60, 1.18)	0.84 (0.49, 1.45)
Early Safety	1114/4386 (25.4%)	276/1391 (19.8%)	0.98 (0.83, 1.15)	0.98 (0.75, 1.27)

AR: Aortic Regurgitation, CAO: Coronary Artery Obstruction, CI: Confidence Interval, MI: Myocardial Infarction, MVC: Major Vascular Complication, PVL: paravalvular leakage.

Table 3. PS adjusted odds ratios (after Bonferroni correction) for each of the considered outcomes in the whole cohort for the sensitivity analysis. Note that the Direct-TAVI group was taken as the reference.

Outcome	**OR (95% CI) Prior & During TAVI BAV (n=507)**	**OR (95% CI) Prior & Not During TAVI BAV (n=197)**	**OR (95% CI) Not Prior & During TAVI BAV (n=4466)**
30-day mortality	1.69 (0.79, 3.59)	1.01 (0.29, 3.49)	1.01 (0.59, 1.75)
MI	1.13 (0.12, 10.32)	NA	0.96 (0.22, 4.15)
Stroke	0.79 (0.24, 2.60)	0.57 (0.07, 4.80)	0.88 (0.42, 1.82)
Moderate/ Severe AR/PVL	1.60 (0.83, 3.07)	0.93 (0.30, 2.89)	1.28 (0.80, 2.06)
CAO	0.23 (0.01, 8.94)	0.61 (0.02, 23.89)	0.81 (0.22, 2.94)
Valve Dysfunction	0.58 (0.19, 1.80)	0.54 (0.06, 4.54)	0.68 (0.34, 1.38)
Pacemaker implantation	0.97 (0.50, 1.87)	0.99 (0.39, 2.50)	1.28 (0.86, 1.89)
Device Migration	1.54 (0.38, 6.23)	1.10 (0.13, 9.74)	1.16 (0.46, 2.91)
Dialysis	1.02 (0.41, 2.53)	0.98 (0.30, 3.23)	0.91 (0.52, 1.58)
MVC	0.66 (0.23, 1.90)	0.82 (0.19, 3.47)	0.83 (0.46, 1.50)
Early Safety	0.97 (0.62, 1.52)	0.87 (0.43, 1.74)	0.94 (0.71, 1.26)

CI: Confidence Interval, MI: Myocardial Infarction, AR: Aortic Regurgitation, PVL: paravalvular leakage, CAO: Coronary Artery Obstruction, MVC: Major Vascular Complication

Table 4. Crude event rates and PS regression adjusted odds ratios (OR) for each of the considered outcomes by valve type for the main analysis that excluded BAVs conducted prior-to-TAVI.

	SAPIEN Valve patients (n=3201)				CoreValve patients (n=2467)			
Outcome	**During-TAVI BAV (n=2336)**	**Direct TAVI (n=865)**	**PS adjusted OR (95% CI) without Bonferroni correction**	**PS adjusted OR (95% CI) with Bonferroni correction**	**During-TAVI BAV (n=1978)**	**Direct TAVI (n=489)**	**PS adjusted OR (95% CI) without Bonferroni correction**	**PS adjusted OR (95% CI) with Bonferroni correction**
30-day mortality	137/2336 (5.9%)	40/865 (4.6%)	1.13 (0.76, 1.68)	1.13 (0.59, 2.15)	98/1978 (5.0%)	22/489 (4.5%)	0.80 (0.46, 1.38)	0.80 (0.33, 1.93)
MI	17/2322 (0.73%)	6/862 (0.70%)	0.73 (0.27, 2.02)	0.73 (0.14, 3.79)	17/1968 (0.86%)	1/482 (0.21%)	2.17 (0.26, 18.3)	2.17 (0.07, 68.61)
Stroke	55/2325 (2.4%)	23/860 (2.7%)	0.63 (0.37, 1.08)	0.63 (0.26, 1.51)	72/1969 (3.7%)	12/482 (2.5%)	0.97 (0.48, 1.95)	0.97 (0.31, 3.01)
Moderate/	121/2072	32/800	1.11 (0.72,	1.11 (0.55,	306/1830	46/453	1.15 (0.79,	1.15 (0.63,

Severe AR/PVL	(5.8%)	(4.0%)	1.71)	2.23)	(16.7%)	(10.2%)	1.68)	2.12)
CAO	19/2320 (0.82%)	7/860 (0.81%)	0.84 (0.32, 2.19)	0.84 (0.18, 3.97)	14/1970 (0.71%)	5/484 (1.0%)	0.41 (0.13, 1.35)	0.41 (0.06, 2.81)
Valve Dysfunction	50/2315 (2.2%)	14/858 (1.6%)	1.12 (0.58, 2.16)	1.12 (0.39, 3.25)	83/1964 (4.2%)	25/483 (5.2%)	**0.58 (0.34, 0.99)**	0.58 (0.24, 1.40)
PPM	127/2324 (5.5%)	45/858 (5.2%)	1.18 (0.80, 1.76)	1.18 (0.63, 2.24)	363/1967 (18.5%)	67/480 (14.0%)	1.26 (0.91, 1.74)	1.26 (0.74, 2.13)
Device Migration	29/2325 (1.2%)	4/858 (0.47%)	2.65 (0.86, 8.14)	2.65 (0.43, 16.32)	40/1964 (2.0%)	18/481 (3.7%)	0.91 (0.45, 1.83)	0.91 (0.29, 2.83)
Haemofiltration/ Dialysis	116/2311 (5.0%)	44/859 (5.1%)	0.95 (0.64, 1.42)	0.95 (0.50, 1.82)	62/1966 (3.2%)	23/480 (4.8%)	0.91 (0.50, 1.65)	0.91 (0.35, 2.39)
MVC	97/2316 (4.2%)	31/857 (3.6%)	0.98 (0.62, 1.54)	0.98 (0.47, 2.04)	77/1966 (3.9%)	21/483 (4.3%)	0.79 (0.44, 1.40)	0.79 (0.31, 2.01)
Early Safety	573/2282 (25.1%)	154/852 (18.1%)	1.07 (0.86, 1.34)	1.07 (0.75, 1.53)	521/1957 (26.6%)	111/473 (23.5%)	0.85 (0.65, 1.12)	0.85 (0.54, 1.32)

AR: Aortic Regurgitation, CAO: Coronary Artery Obstruction, CI: Confidence Interval, MI: Myocardial Infarction, MVC: Major Vascular Complication, PPM: Pacemaker implantation, PVL: paravalvular leakage

Table 5. PS adjusted odds ratios (after Bonferroni correction) for each of the considered outcomes in the SAPIEN subgroup for the sensitivity analysis. Note that the Direct-TAVI group was taken as the reference.

Outcome	**OR (95% CI) Prior & During TAVI BAV**	**OR (95% CI) Prior & no During TAVI BAV**	**OR (95% CI) no Prior & During TAVI BAV**
30-day mortality	1.71 (0.65, 4.44)	1.10 (0.27, 4.53)	1.08 (0.54, 2.17)
MI	0.84 (0.06, 11.85)	NA	0.70 (0.11, 4.23)
Stroke	0.84 (0.20, 3.50)	0.51 (0.04, 6.99)	0.61 (0.23, 1.58)
Moderate/ Severe AR/PVL	1.36 (0.47, 3.92)	1.15 (0.25, 5.32)	1.13 (0.53, 2.41)
CAO	NA	0.82 (0.02, 36.94)	0.83 (0.15, 4.59)
Valve Dysfunction	0.95 (0.16, 5.73)	0.47 (0.01, 18.03)	0.99 (0.31, 3.12)
Pacemaker implantation	0.91 (0.28, 2.95)	1.43 (0.39, 5.20)	1.13 (0.57, 2.25)
Device Migration	5.91 (0.53, 65.82)	NA	2.79 (0.38, 20.74)
Haemofiltration/ Dialysis	1.03 (0.34, 3.12)	1.23 (0.34, 4.50)	1.01 (0.50, 2.03)
MVC	0.49 (0.11, 2.29)	0.74 (0.11, 5.02)	0.94 (0.42, 2.09)
Early Safety	1.01 (0.56, 1.83)	1.03 (0.45, 2.39)	1.03 (0.70, 1.52)

CI: Confidence Interval, MI: Myocardial Infarction, AR: Aortic Regurgitation, PVL: paravalvular leakage, CAO: Coronary Artery Obstruction, MVC: Major Vascular Complication

Table 6. PS adjusted odds ratios (after Bonferroni correction) for each of the considered outcomes in the CoreValve subgroup for the sensitivity analysis. Note that the Direct-TAVI group was taken as the reference.

Outcome	**OR (95% CI) Prior & During TAVI BAV**	**OR (95% CI) Prior & no During TAVI BAV**	**OR (95% CI) no Prior & During TAVI BAV**
30-day mortality	1.71 (0.46, 6.42)	0.84 (0.06, 12.13)	0.86 (0.33, 2.26)
MI	NA	NA	2.91 (0.06, 137.8)
Stroke	0.48 (0.05, 5.09)	NA	0.96 (0.28, 3.30)
Moderate/ Severe AR/PVL	1.90 (0.77, 4.65)	0.68 (0.12, 4.00)	1.13 (0.58, 2.17)
CAO	0.40 (0.01, 22.63)	NA	0.46 (0.06, 3.78)
Valve Dysfunction	0.60 (0.14, 2.62)	0.64 (0.04, 9.23)	0.55 (0.21, 1.44)
Pacemaker implantation	1.14 (0.45, 2.86)	0.80 (0.18, 3.63)	1.26 (0.71, 2.23)
Device Migration	1.21 (0.15, 10.03)	1.34 (0.12, 15.03)	0.89 (0.26, 3.06)
Haemofiltration/ Dialysis	0.84 (0.13, 5.51)	0.37 (0.01, 14.33)	0.88 (0.31, 2.53)
MVC	0.75 (0.14, 4.00)	1.43 (0.15, 13.91)	0.74 (0.27, 2.07)
Early Safety	0.98 (0.47, 2.05)	0.69 (0.18, 2.61)	0.82 (0.51, 1.34)

CI: Confidence Interval, MI: Myocardial Infarction, AR: Aortic Regurgitation, PVL: paravalvular leakage, CAO: Coronary Artery Obstruction, MVC: Major Vascular Complication