Preoperative Atrial Fibrillation is associated with long-term morTality in patients undergoing suRgical AortiC valvE Replacement

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Abstract

Introduction Atrial fibrillation (AF) is frequent after any cardiac surgery, but evidence suggests it may have no significant impact on survival if sinus rhythm (SR) is effectively restored early after the onset of the arrhythmia. In contrast, management of preoperative AF is often overlooked during or after cardiac surgery despite several proposed protocols. This study sought to evaluate the impact of preoperative AF on mortality in patients undergoing isolated surgical aortic valve replacement (AVR). Methods We performed a retrospective, single-centre study involving 2,628 consecutive patients undergoing elective, primary isolated surgical AVR from 2008 to 2018. A total of 268/ 2,628 patients (10.1%) exhibited AF before surgery. The effect of preoperative AF on mortality was evaluated with univariate and multivariate analyses. Results Short-term mortality was 0.8% and was not different between preoperative AF and SR cohorts. Preoperative AF was highly predictive of long-term mortality (median follow-up of 4 years [Q1-Q3 2-7]; HR: 2.24, 95% CI: 1.79-2.79, P<0.001), and remained strongly and independently predictive after adjustment for other risk factors (HR: 1.54, 95% CI: 1.21-1.96, P<0.001) compared with preoperative SR. In propensity score-matched analysis, the adjusted mortality risk was higher in the AF cohort (OR: 1.47, 95% CI: 1.04-1.99, P=0.03) compared with the SR cohort. Conclusions Preoperative AF was independently predictive of long-term mortality in patients undergoing isolated surgical AVR. It remains to be seen whether concomitant surgery or other preoperative measures to correct AF may impact long-term survival.

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ABSTRACT

Introduction

Atrial fibrillation (AF) is frequent after any cardiac surgery, but evidence suggests it may have no significant impact on survival if sinus rhythm (SR) is effectively restored early after the onset of the arrhythmia. In contrast, management of preoperative AF is often overlooked during or after cardiac surgery despite several proposed protocols. This study sought to evaluate the impact of preoperative AF on mortality in patients undergoing isolated surgical aortic valve replacement (AVR).

Methods

We performed a retrospective, single-centre study involving 2,628 consecutive patients undergoing elective, primary isolated surgical AVR from 2008 to 2018. A total of 268/ 2,628 patients (10.1%) exhibited AF before surgery. The effect of preoperative AF on mortality was evaluated with univariate and multivariate analyses.

Results

Short-term mortality was 0.8% and was not different between preoperative AF and SR cohorts. Preoperative AF was highly predictive of long-term mortality (median follow-up of 4 years [Q1-Q3 2-7]; HR: 2.24, 95% CI: 1.79-2.79, P<0.001), and remained strongly and independently predictive after adjustment for other risk factors (HR: 1.54, 95% CI: 1.21-1.96, P<0.001) compared with preoperative SR. In propensity score-matched analysis, the adjusted mortality risk was higher in the AF cohort (OR: 1.47, 95% CI: 1.04-1.99, P=0.03) compared with the SR cohort.

Conclusions

Preoperative AF was independently predictive of long-term mortality in patients undergoing isolated surgical AVR. It remains to be seen whether concomitant surgery or other preoperative measures to correct AF may impact long-term survival.

Key words: atrial fibrillation, aortic valve replacement, mortality

ABBREVIATIONS

AF: atrial fibrillation

AVR: aortic valve replacement

SR: sinus rhythm

TAVI: transcatheter aortic valve implantation

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Despite advancements in screening, diagnosis and management, the presence of AF is still associated with an increased risk of stroke, heart failure and death. New-onset AF is frequent after any cardiac surgery, but evidence suggests it has no significant impact on survival if sinus rhythm (SR) is effectively restored early after the onset of the arrhythmia. In contrast, several studies have suggested that preoperative AF is associated with increased morbidity and mortality in patients undergoing cardiac surgery. Management of preoperative AF is often overlooked during or after cardiac surgery despite several proposed protocols. Concomitant surgical AF ablation is recommended to improve left ventricular ejection fraction, exercise tolerance, and long-term survival, and to reduce the risk of stroke and thromboembolic events. However, the presumed additional risk of atriotomy and subsequent surgical ablation still precludes its routine use in a large subset of patients.

AF is common in patients with aortic valve disease, especially aortic stenosis. This is, at least in part, because the incidence of both conditions increases with age. Furthermore, chronically elevated left ventricular afterload secondary to aortic stenosis precipitates impaired diastolic relaxation with resultant upstream transfer of pressure to the left atrium, which provokes left atrial dilatation, fibrosis and arrhythmogenesis . A recent metanalysis suggested an association between preoperative AF and adverse outcomes after surgical aortic valve replacement (AVR). Of note, patients with AF are usually older with multiple comorbidities. They also often require concomitant cardiac surgeries such as coronary artery bypass graft and other valve surgeries. Thus, there is still some debate whether AF is an independent predictor of adverse prognosis after surgical AVR or whether the worse prognosis among AF patients rather reflects increased age and associated comorbidities and/or concomitant surgeries. The AF-TRACER study sought to evaluate the sole impact of preoperative AF on mortality in a large cohort of patients undergoing isolated surgical AVR.

METHODS

Study design

The AF-TRACER study is a single-centre, retrospective observational study conducted at the Royal Papworth Hospital, Cambridge, UK. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Anonymised data were obtained from the institutional electronic database normally utilized for patient care and therefore the need for informed consent was waived by the institutional Medical Ethical Committee. Baseline, rhythm analysis, operative, and outcome data were prospectively collected, validated and entered into the administrative database, which was analysed retrospectively.

Study population

Between July 2008 and July 2018, 2,628 consecutive patients underwent first-time, elective isolated surgical AVR using a mechanical or stented biological valve prosthesis. Patients with concomitant cardiac surgeries, previous cardiac surgery, urgent/emergency surgeries, or transthoracic echocardiography showing other significant valve abnormalities apart from those concerning the aortic valve were excluded. Preoperative AF was documented on a 12-lead electrocardiogram and/or Holter recording within the 3 months prior to surgery. There was no distinction made between preoperative paroxysmal or persistent AF. Data on the duration of AF diagnosis were not available. The AVR was performed according to standard of care and in line with local protocols. In addition to patient's preference, the cut-off age for using mechanical versus biological prosthesis was dictated according to updated practice guidelines.

Study outcomes

Short-term mortality was defined as in-hospital death or death occurring within 30 days of surgery. Long-term all-cause mortality was defined as death occurring due to any cause up until documented longest follow-up.

Statistical analysis

Paired and unpaired t tests were used for comparison of normally distributed and Wilcoxon rank sum test used for non-normally distributed variables. Where necessary, log transformations were employed. Data are presented as mean (standard deviation) or median (Q1–Q3). Dichotomous variables were compared using $\chi 2$ test or Fisher's exact test, as appropriate. The Kaplan-Meier survival methods with log-rank tests were used. The patients were divided into 2 groups; (1) preoperative SR group, and (2) preoperative AF group. To investigate the relationship between preoperative AF and long-term mortality, univariate and multivariable hazard regression models of Cox were used. The bootstrap technique using one thousand samples was used as a way to account for final multivariable model uncertainty. All study variables were first analysed with univariate analysis and those that showed a significant interaction ($P< 0.1$) were entered into the final multivariable analysis. Furthermore, we performed propensity score matching analysis with 1:1 matching followed by logistic regression analysis to estimate the average treatment effect adjusted for baseline differences (namely age, gender, hypertension, diabetes mellitus, chronic pulmonary disease, peripheral vascular disease, previous myocardial infarction, perioperative creatinine level and left ventricular function) between the two groups of interest. The coefficients were converted to odds ratios for interpretation. A P-value of <0.05 was considered statistically significant. Analyses were performed with Stata V.15 (StataCorp, College Station, Texas).

RESULTS

Characteristics of the study population

A total of 2,628 consecutive patients were included in the study with 268 patients (10.1%) exhibiting AF before surgical AVR. Baseline patient characteristics are shown in Table 1. Patients who had preoperative AF were older and more often received bioprostheses rather than mechanical AVR. These individuals had a higher prevalence of risk factors including hypertension, diabetes mellitus, peripheral vascular disease, previous myocardial infarction, raised preoperative serum creatinine, and poor left ventricular function (defined as left ventricular ejection fraction <30% as assessed by transthoracic echocardiography) compared with patients who had preoperative SR [Table 1]. The patients were followed up for a median of 1508 [790–2611] days, approximately 4 [2–7] years.

AF and short-term mortality

Median in-hospital stay was 7 [6–10] days and was significantly longer in the AF cohort compared with SR cohort (9 [7–13] vs. 7 [6–10] days, P<0.001). Twenty patients (0.8%) died within 30 days of surgery (1 patient in AF group [0.4%] vs. 19 patients in SR group [0.8%], P=0.714). All early deaths were from cardiovascular-related causes (i.e. sudden death, fatal myocardial infarction, stroke, pump failure or fatal arrhythmia).

AF and long-term mortality

All-cause mortality occurred in 568 out of 2,628 patients (21.6%) at a median follow-up of 4 [2-7] years. Preoperative AF was highly predictive of mortality (97/ 268 (36.1%) deaths in AF group vs 471/ 2,360 (19.9%) in SR group; HR: 2.24, 95% CI: 1.79-2.79, P<0.001). The Kaplan-Meier survival curves separated early and the difference remained constant for up to 10 years follow-up [Figure 1].

Of the baseline characteristics in Table 1, the following were associated with long-term all-cause mortality using univariate hazard regression model of Cox: increasing age (HR: 1.07, 95% CI: 1.06-1.08, P<0.001), bioprostheses (HR: 3.30, 95% CI: 2.28-4.77, P<0.001), hypertension (HR: 1.37, 95% CI: 1.14-1.63, P<0.001), diabetes (HR: 1.59, 95% CI: 1.31-1.95, P<0.001), raised preoperative serum creatinine (HR: 1.006, 95% CI: 1.005-1.007, P<0.001), chronic pulmonary disease (HR: 1.56, 95% CI: 1.29-1.89, P<0.001), peripheral vascular disease (HR: 2.03, 95% CI: 1.55-2.66, P<0.001), previous myocardial infarction (HR: 1.59, 95% CI: 1.16-2.17, P=0.006), poor left ventricular function (HR: 1.66, 95% CI: 1.24-2.23, P=0.002), and high EuroSCORE I (HR: 1.29, 95% CI: 1.26-1.34, P<0.001) [Supplemental table 1].

The following variables were then entered into the final baseline multivariate Cox proportional hazard model: age, hypertension, diabetes, preoperative serum creatinine, chronic pulmonary disease, peripheral vascular

disease, pervious myocardial infarction, and left ventricular function. We did not include bioprostheses in the model, as we felt this reflects advanced age in the preoperative AF group rather than being a genuine risk factor. Similarly, we did not include EuroSCORE I in the model as we felt it would be a repetition, since EuroSCORE I incorporates risk factors already included in the model, such as age, chronic pulmonary disease, peripheral vascular disease, serum creatinine and left ventricular function. Multivariate analysis showed that AF remained significantly associated with long-term all-cause mortality after adjustment for other risk factors (HR: 1.54, 95% CI: 1.21-1.96, P<0.001) and after bootstrap resampling, the optimism-corrected c-index was -0.012 and the calibration slope was 0.906, which suggests no over fitting of the model. Other independent predictors of long-term mortality included advanced age (HR: 1.06, 95% CI: 1.05-1.08, P<0.001), presence of diabetes (HR: 1.46, 95% CI: 1.18-1.80, P=0.001), chronic pulmonary disease (HR: 1.44, 95% CI: 1.17-1.77, P=0.001), peripheral vascular disease (HR: 1.48, 95% CI: 1.11-1.97, P=0.001), poor left ventricular function (HR: 1.47, 95% CI: 1.04-2.08, P=0.031) and raised preoperative serum creatinine (HR: 1.005 95% CI: 1.003-1.007, P<0.001).

In a propensity score matching analysis, the risk of long-term all-cause mortality was higher in the preoperative AF cohort (OR: 1.47, 95% CI: 1.04-1.99, P=0.031) compared with the preoperative SR cohort after adjustment of baseline differences between the two groups [Supplemental Table 2, Supplement Table 3 and Supplemental Figure 1].

DISCUSSION

The main finding of this single-centre, retrospective large-cohort study is that preoperative AF is independently predictive of long-term all-cause mortality at a median follow-up of 4 years and remained independently predictive after adjustment for other risk factors and in propensity score-matched analysis following first-time isolated surgical AVR.

Our study further lends support to previous studies investigating the relationship between preoperative AF and mortality after AVR. Ngaage and colleagues demonstrated an increased risk of major adverse cardiovascular events with preoperative AF in 381 patients undergoing surgical AVR, however preoperative AF was not predictive of all-cause long-term mortality after risk factors adjustment, which was probably due to the small sample size. Saxena and colleagues showed that preoperative AF significantly increases the risk of all-cause mortality by 36% after surgical AVR. However, intraoperative variables such as bypass time and aortic clamp time were not adjusted for in their analysis, despite the bypass time being significantly different between the study groups. These important variables have been shown to affect clinical outcomes following cardiac surgery. Of note, there was no significant difference between the bypass time and aortic clamp time between the two cohorts in our study (Table 1). Levy and colleagues found that preoperative AF was independently associated with more than 5-fold increase in long-term mortality (HR 5.5, 95% CI, 1.13-26.15; P=0.03), however, the study involved only 83 patients undergoing surgical AVR, all with poor left ventricular function. The remarkable hazard ratio expressed in Levy's analysis likely reflects the well-documented fact that AF is poorly tolerated and portends a worse prognosis in patients with congestive heart failure. Transcatheter aortic valve implantation (TAVI) is currently the gold standard intervention for non-surgical candidates with aortic valve stenosis. A meta-analysis of observational studies found that preoperative AF significantly increases the risk of long-term all-cause and cardiovascular mortality after TAVI.

Wang and colleagues demonstrated that preoperative AF was a predictor of 30-day mortality after surgical AVR. In our study, patients who had preoperative AF were significantly older with more comorbidities such as hypertension, diabetes, peripheral vascular disease, previous myocardial infarction, renal disease and left ventricular dysfunction compared with patients who had preoperative SR. This is probably the reason for the prolonged in-hospital stay observed in the preoperative AF cohort. However, we observed no significant difference in the operative or 30-day mortality between the 2 study groups. One plausible explanation is that our study only included patients undergoing elective surgery whereas 62% of Wang et al.'s preoperative AF cohort had urgent or emergency surgery compared with 48% in the preoperative SR cohort (P=0.008). Urgent or emergency surgery was predictive of morbidity and mortality during follow-up.

Our results suggest that preoperative AF has no value in formalized surgical risk-stratifying tools, such as the EuroSCORE, as we did not find *in-hospital* mortality to be impacted by preoperative AF. There is scope, however, for preoperative AF to be incorporated into long-term surgical risk assessments, or at least to inform decision-making when counselling patients as to the risk of AVR in the outpatient setting. Of greater clinical interest is whether restoration of SR pre- or perioperatively reverses the risk attributable to preoperative AF. This is yet to be determined and represents a highly worthwhile area for further studies.

Study limitations

This is a retrospective observational study, and therefore, has inherent limitations of the retrospective design. There are a few other important limitations. First, the study is subjected to differences over time in individual surgical techniques and operative management. Second, preoperative AF type (paroxysmal or persistent) was not classified, however even patients with paroxysmal AF undergoing surgical AVR appear to be at higher risk of developing persistent AF and death at 12 months follow-up compared with patients with preoperative sinus rhythm. Third, patients with postoperative new-onset AF had either spontaneous recovery of sinus rhythm or successful cardioversion before hospital discharge, or, less frequently, were discharged on anticoagulation therapy if remained in AF. This is unlikely to affect the results as the study focuses on the preoperative rhythm state. Fourth, data on long-term anticoagulation for AF thromboprophylaxis were not available. This is potentially an important confounder, as appropriate provision of anticoagulation to mitigate thromboembolic events in those with atrial arrhythmias has been demonstrated to reduce mortality Fifth, whilst our long-term analysis reports all-cause mortality, and thus deaths unrelated to preoperative AF might have been included, all-cause mortality is considered an appropriate endpoint to follow in the long-term as it accounts for both cardiac and systemic diseases and is unaffected by any reporting or misclassification bias.

CONCLUSIONS

Preoperative AF is independently predictive of long-term all-cause mortality in patients undergoing isolated surgical AVR. It remains to be seen in prospective studies whether concomitant surgical ablation or other preoperative measures to correct AF may impact long-term survival.

Author contributions:

Author	Role
Mohamed Farag	Concept/design, Data analysis/interpretation ,Drafting article, Critical revision of article, Approval of a
Yusuf Kiberu	Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics
S Ashwin Reddy	Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics
Ahmad Shoaib	Data analysis/interpretation , Drafting article, Critical revision of article, Approval of article , Statistics
Mohaned Egred	Drafting article, Critical revision of article, Approval of article, Statistics
Unni Krishnan	Concept/design, Data analysis/interpretation, Critical revision of article, Approval of article, Statistics
Mina Fares	Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics
Marta Peverelli	Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics,
Diana A Gorog	Data analysis/interpretation, Drafting article, Critical revision of article, Approval of article, Statistics,
Walid Elmahdy	Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of a
Marius Berman	Concept/design, Data analysis/interpretation,Critical revision of article, Approval of article
Samer Nashef	Concept/design, Critical revision of article, Approval of article
Mohamed Osman	Concept/design, Data analysis/interpretation, Drafting article, Critical revision of article, Approval of a

REFERENCES

Table 1: Baseline Patient Characteristics

	Preoperative SR (n=2360)	**Preoperative AF (n=268)**	**P Value**
Age, years	71±11	77±7	**<0.001**
Female	1126 (47.7)	113 (42.2)	0.093
Body Mass Index (kg/m²)	28.6±5.6	28.7±5.7	0.808
AVR prosthesis type			
Biological	2052 (86.9)	248 (92.5)	**0.008**
Mechanical	308 (13.1)	20 (7.5)	
AVR bypass time, min	74±26	73±25	0.795
AVR aortic clamp time, min	54±17	53±16	0.360
Aortic valve pathology			
Aortic stenosis	2237 (94.8)	259 (96.6)	0.237
Aortic regurgitation	123 (5.2)	9 (3.4)	
Hypertension	1396 (59.2)	202 (75.4)	**<0.001**
Diabetes mellitus	402 (17.0)	60 (22.4)	**0.034**
Πρεοπερατιε σερυμ ςρεατινινε (μμολ/Λ)	92±35	105±43	**<0.001**
Chronic pulmonary disease	425 (18.0)	61 (22.8)	0.067
Peripheral vascular disease	150 (6.4)	33 (12.3)	**<0.001**
Current smoker	125 (5.3)	10 (3.7)	0.309
Cerebral vascular accident	63 (2.7)	13 (4.9)	0.053
Previous myocardial infarction	143 (6.1)	27 (10.1)	**0.017**
Poor left ventricular function (EF <30%) *	121 (5.1)	38 (14.2)	**<0.001**
Reoperation for any reason +	33 (1.4)	6 (2.2)	0.281
Pacemaker placement during index admission	61 (2.6)	11 (4.1)	0.164
EuroSCORE I	6.3±2.4	7.9±2.4	**<0.001**
Logistic EuroSCORE	7.4±6.7	11.9±9.5	**<0.001**

Values presented as mean±SD or n (%)

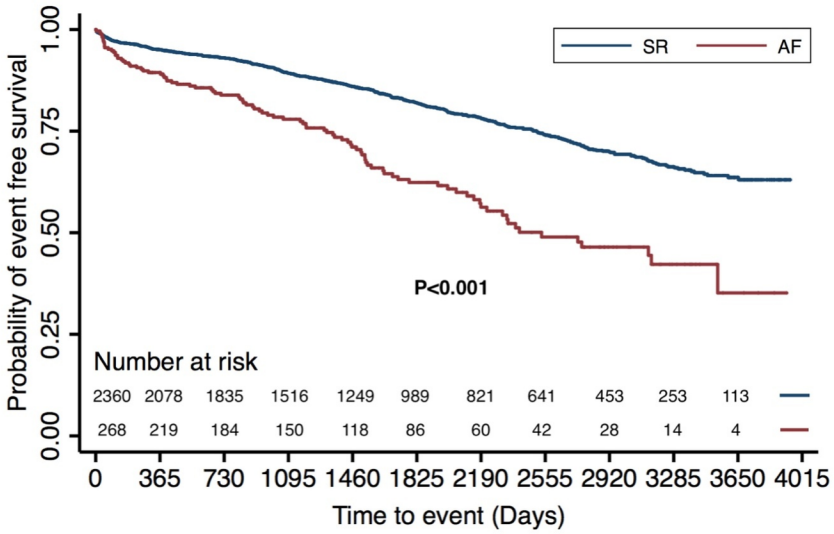
AF: atrial fibrillation, AVR: aortic valve replacement, EF: ejection fraction, SR: sinus rhythm

* Measured by transthoracic echocardiography in all patients within the 3 months preceding surgery.

+ Reoperation reasons included structural valve degeneration, valve thrombosis or infective endocarditis.

Figure 1: Kaplan-Meier survival curves showing significantly lower event free survival in patients with preoperative atrial fibrillation prior to surgical aortic valve replacement

Preoperative atrial fibrillation (AF) was highly associated with long-term all-cause mortality with a hazard ratio of 2.2 and remained strongly and independently associated after adjustment for other risk factors. SR: sinus rhythm



Supplemental table 1: Factors associated with long-term all-cause mortality using univariate hazard regression model of Cox

	Hazard Ratio (95% confidence interval)	**P Value**
Age	**1.07 (1.06-1.08)**	**<0.001**
Female	1.14 (0.96-1.34)	0.131
Body mass index	5.94 (0.08-6.91)	0.187
Biological AVR type	**3.30 (2.28-4.77)**	**<0.001**
AVR bypass time, min	1.00 (0.99-1.005)	0.226
AVR aortic clamp time, min	0.99 (0.98-1.004)	0.771
Aortic valve pathology	0.93 (0.83-1.04)	0.210
Hypertension	**1.37 (1.14-1.63)**	**<0.001**
Diabetes mellitus	**1.59 (1.31-1.95)**	**<0.001**
Preoperative serum creatinine	**1.006 (1.005-1.007)**	**<0.001**
Chronic pulmonary disease	**1.56 (1.29-1.89)**	**<0.001**
Peripheral vascular disease	**2.03 (1.55-2.66)**	**<0.001**
Current smoker	1.14 (0.97-1.31)	0.176
Cerebral vascular accident	1.31 (0.84-2.05)	0.256
Previous myocardial infarction	**1.59 (1.16-2.17)**	**0.006**
Poor left ventricular function (EF <30%)	**1.66 (1.24-2.23)**	**0.002**
Reoperation for any reason	1.56 (0.89-2.24)	0.198

	Hazard Ratio (95% confidence interval)	**P Value**
Pacemaker placement during index admission	2.34 (0.43-3.78)	0.212
EuroSCORE I	**1.29 (1.26-1.34)**	**<0.001**

AVR: aortic valve replacement, EF: ejection fraction

Supplemental Table 2: Propensity score-matched analysis with average treatment effects

Outcome	**Group**	**Coefficient (95% CI)**	**Odds Ratio* (95% CI**
Long-term all-cause mortality	Group 1: preoperative SR	Reference	
	Group 2: preoperative AF	0.0693236 (0.0061877 to 0.1324595)	1.47 (1.04 – 1.99)

***** Adjusted for age, gender, hypertension, diabetes, preoperative serum creatinine, chronic pulmonary disease, peripheral vascular disease, previous myocardial infarction, and left ventricular function.

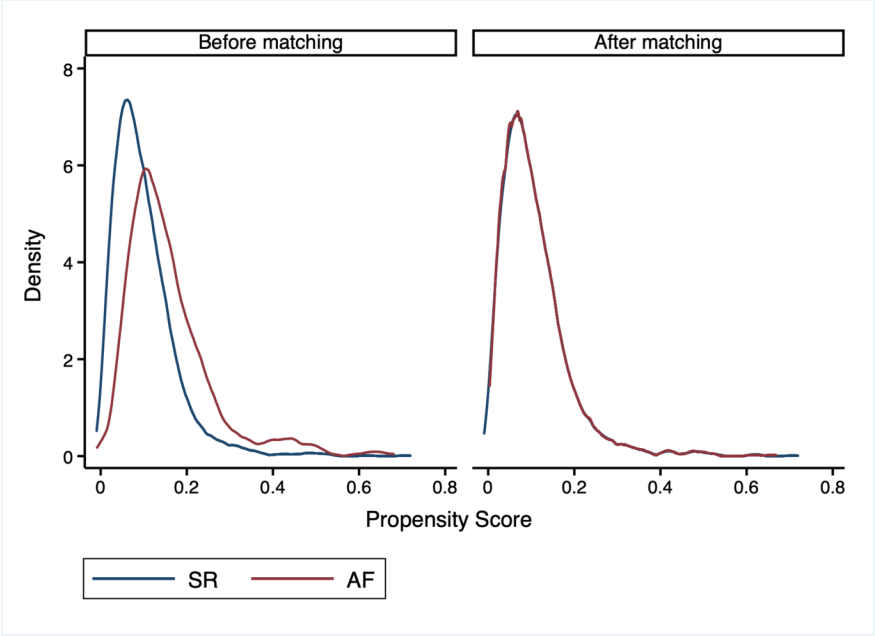
AF: atrial fibrillation, SR: sinus rhythm

Supplement Table 3: Baseline patient characteristics: propensity score-matched cohort

Variables	**Standardized differences**	**Standardized differences**	**Variance ratio**	**Varia**
	Raw	**Matched**	**Raw**	**Matc**
Age (years)	0.59	-0.03	0.43	0.79
Gender	-0.10	-0.10	0.98	0.98
Hypertension	0.34	-0.05	0.76	1.02
Diabetes mellitus	0.13	-0.03	1.23	0.95
Preoperative serum creatinine	0.35	0.20	1.47	0.88
Chronic pulmonary disease	0.11	0.07	1.18	1.11
Peripheral vascular disease	0.20	-0.02	1.77	0.94
Previous myocardial infarction	0.14	-0.05	1.55	0.84
Poor left ventricular function	0.31	0.04	2.52	1.17

Supplemental Figure 1: Overlay of Kernel density distributions of preoperative sinus rhythm (SR) and atrial fibrillation (AF) propensity scores before and after propensity score matching

There was a common support area to perform propensity score matching, and participants were predominately matched within the common region.



Key question

Does AF affects mortality after AVR

Key findings

Preoperative AF was independently predictive of long-term mortality in patients undergoing isolated surgical AVR

Take-home message

Pre-operative AF should be included in decision-making when counselling patients as to the risk of AVR in the outpatient setting