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ORIGINAL RESEARCH

Patients with Atrial Fibrillation Benefit from SAVR with Surgical Ablation Compared to TAVR Alone

William L. Patrick · Zehang Chen · Jason J. Han · Benjamin Smood · Akhil Rao · Fabliha Khurshan · Siddharth Yarlagadda · Amit Iyengar · John J. Kelly · Joshua C. Grimm · Marisa Cevasco · Joseph E. Bavaria · Nimesh D. Desai

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ABSTRACT

Introduction: In patients with preoperative atrial fibrillation (AF) undergoing aortic valve replacement, the addition of surgical ablation to surgical aortic valve replacement (SAVR-SA) is efficacious and a Class I guideline. We hypothesized that this subgroup may benefit from SAVR-SA compared to transcatheter aortic valve replacement (TAVR) alone.

Methods: Medicare beneficiaries with persistent non-valvular AF who underwent SAVR-SA or TAVR alone between 2012 and 2018 were included. Patients with high-risk surgical comorbidities were excluded. Groups were matched using inverse probability weighting. The primary outcome was all-cause mortality. Secondary outcomes were stroke, transient ischemic attack, permanent pacemaker implantation, bleeding, rehospitalization for atrial arrhythmias, and rehospitalization for heart failure. Kaplan–Meier estimates and Cox proportional-hazards regression were used to compare outcomes. Outcomes were adjusted for variables with a standardized mean difference greater than 0.1.

Results: Of 439,492 patients who underwent aortic valve replacement, 2591 underwent SAVR-SA and 1494 underwent TAVR alone. Weighting resulted in adequately matched groups. Compared to TAVR alone, SAVR-SA was associated with a significant reduction in all-cause mortality (HR 0.65, 95% CI 0.53–0.79), permanent pacemaker implantation (HR 0.62, 95% CI 0.44–0.87), bleeding (HR 0.63, 95% CI 0.39–1.00), and rehospitalization for heart failure (HR 0.49 (0.36–0.65). There was no difference in the incidence of stroke (HR 1.07, 95% CI 0.74–1.54), transient ischemic attack (HR 1.05, 95% CI 0.75–1.47), or rehospitalization for atrial arrhythmia.

Conclusion: Select patients with persistent non-valvular AF may benefit from SAVR-SA compared to TAVR alone.

Keywords: Surgical aortic valve replacement; SAVR; Transcatheter aortic valve replacement;

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W. L. Patrick (✉) · Z. Chen · J. J. Han · B. Smood · F. Khurshan · S. Yarlagadda · A. Iyengar · J. J. Kelly · J. C. Grimm · M. Cevasco · J. E. Bavaria · N. D. Desai
Division of Cardiovascular Surgery, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104, USA
e-mail: william.patrick@pennmedicine.upenn.edu

W. L. Patrick · N. D. Desai
Leonard Davis Institute, University of Pennsylvania, Philadelphia, PA, USA

W. L. Patrick · N. D. Desai
Penn Cardiovascular Outcomes, Quality, and Evaluative Research Center, Philadelphia, PA, USA

TAVR; Atrial fibrillation; Ablation; Surgical ablation

Key Summary Points

The addition of surgical ablation to surgical aortic valve replacement (SAVR) in those with atrial fibrillation is effective and is a Class 1 Level B recommendation from Society of Thoracic Surgeons.

Surgical ablation in patients with atrial fibrillation cannot be readily performed in those undergoing transcatheter aortic valve replacement (TAVR).

With the expanding role of TAVR in low-risk patients, do those with atrial fibrillation who require aortic valve replacement benefit from SAVR with concomitant surgical ablation compared to TAVR alone?

Patients with intermediate- and low-risk characteristics and atrial fibrillation who undergo SAVR with surgical ablation have better mid-term survival compared to those who undergo TAVR alone.

Patients with intermediate- and low-risk characteristics and atrial fibrillation who undergo SAVR with surgical ablation experience lower rates of pacemaker implantation, bleeding, and rehospitalization compared to those who undergo TAVR alone.

INTRODUCTION

Atrial fibrillation (AF) afflicts approximately five million Americans, a number expected double over the next 25 years [1]. The diagnosis of AF confers significant long-term health risks through a combination of atrioventricular desynchrony, use of anticoagulation, and association with comorbid diseases [2]. The presence of AF before or after cardiac surgery similarly portends higher risks of short- and long-term adverse outcomes, including mortality [3]. The addition of concomitant surgical ablation (SA) of AF during cardiac surgery has been shown to improve long-term survival and freedom from adverse events without compromising short-term outcomes. Initially, the best evidence for this was in the setting of mitral valve surgery, but has since expanded to other operations including surgical aortic valve replacement (SAVR) [4–12]. As such, there is a Class I Level B recommendation from Society of Thoracic Surgeons to perform SAVR with concomitant SA (SAVR-SA) in patients with AF undergoing aortic valve replacement [13].

For most patients 65–80 years old who require aortic valve replacement, both transcatheter aortic valve replacement (TAVR) and SAVR have a Class I indication from the American College of Cardiology/American Heart Association [14]. Though AF also confers a higher risk for adverse outcomes after TAVR, concomitant complete endocardial and epicardial ablation is not performed during a TAVR [15–18]. Optimal treatment for low- and intermediate-risk patients with AF who require aortic valve replacement is an area of uncertainty [19].

We hypothesize that SAVR-SA is associated with better outcomes in select patients with persistent non-valvular AF compared to TAVR alone.

METHODS

All Medicare beneficiaries in the Centers for Medicare & Medicaid Services MEDPAR files were evaluated for inclusion. The MEDPAR files contain information for all beneficiaries who use inpatient services. Those at least 18 years old who underwent aortic valve replacement between 2012 and 2018 were included. Diagnoses and procedures were identified using International Classification of Disease (ICD) code versions 9 and 10 (Supplementary Material Table 1). Specific ICD-9 codes were adapted from those used in a recent high-quality manuscript by Rankin et al. on surgical AF ablation in coronary artery bypass surgery [20].

Specific ICD-10 codes were selected via an ICD-9 crosswalk.

Patients without persistent AF were excluded. Subtype of AF is not specified within the ICD-9 system. Therefore, the definition of persistent AF used by the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines was adapted to fit claims data [1]. Patients were diagnosed with persistent AF if there was a diagnosis of any AF recorded in at least two of the following scenarios more than 7 days apart: (1) on index admission, (2) at an outpatient hospitalization in the 12 months prior to the index admission, or (3) at an inpatient hospitalization claim in the 12 months prior to the index admission.

Patients with tricuspid and mitral valve disorders were excluded. Those with prior procedures for AF or elimination of the left atrial appendage were excluded. Patients with a history of cardiac surgery or those who underwent concomitant procedures, including coronary artery bypass grafting, were excluded. Patients with medical comorbidities associated with high surgical risk were excluded. A rationale for these exclusions can be found in the "Discussion" section.

Patients were categorized as having undergone TAVR or SAVR. Those who underwent SAVR without SA during the index admission were excluded. The primary endpoint was all-cause mortality. Mortality was obtained from Medicare denominator files. Secondary endpoints were transient ischemic attack, stroke, pacemaker implantation, bleeding, rehospitalization for atrial arrhythmia, and rehospitalization for heart failure.

The Elixhauser Comorbidity Index was used to assess comorbidities. CHA_2DS_2-VASc and HAS-BLED risk scores were also calculated for each patient. Standard descriptive statistics were used to summarize characteristics of the sample population. Characteristics of the two treatment groups were compared using the standardized mean difference (Cohen's *d*). Race and year of operation were compared using a Pearson's chi-squared test.

Treatment groups were matched using inverse probability of treatment weighting in which propensity scores were calculated using a generalized boosted regression model. All Elixhauser comorbidities as well as age, CHA_2DS_2-VASc, and HAS-BLED risk score were included in this model. Balance between treatment groups was assessed using standardized mean differences. A standardized difference of 0.1 or less was deemed to be an ideal balance, and a standardized difference of 0.2 or less was deemed to be an acceptable balance [21].

Kaplan–Meier estimates of survival or cumulative incidence for the primary and secondary outcomes were calculated and displayed. The competing risk of death was accounted for in each secondary endpoint analysis. Each treatment group was compared using a Cox proportional-hazards model with and without variables that differed between matched groups by a standardized mean difference of greater than 0.1. Landmark analysis for rehospitalization for atrial arrhythmias and for heart failure was performed with a landmark time of 180 days after the index operation. Rehospitalization for sepsis was analyzed as a falsification endpoint.

Matching was performed using the "twang" package in R statistics, version 3.6.2 (R Foundation). Data management and analyses were performed using STATA, version 16.1 (College Station, Texas). Code files are provided (Supplementary Material). This project (protocol number 849385) was reviewed the IRB at the University of Pennsylvania and deemed exempt from approval according to 45 CFR 46.104, category 4.

RESULTS

Of the 439,492 patients who underwent aortic valve replacement, 7516 underwent SAVR and 1494 underwent TAVR (Fig. 1). Among patients who underwent SAVR, 34% (2591/7516) underwent SAVR-SA. The proportion patients with AF who underwent SAVR-SA as opposed to TAVR alone steadily decreased from 86% in 2012 to 33% in 2018 (χ^2 (1, N = 4100) = 2854, $p < 0.01$) (Fig. 2). At baseline, patients undergoing TAVR were older and had a higher incidence of comorbidities compared to those undergoing SAVR-SA (Table 1).

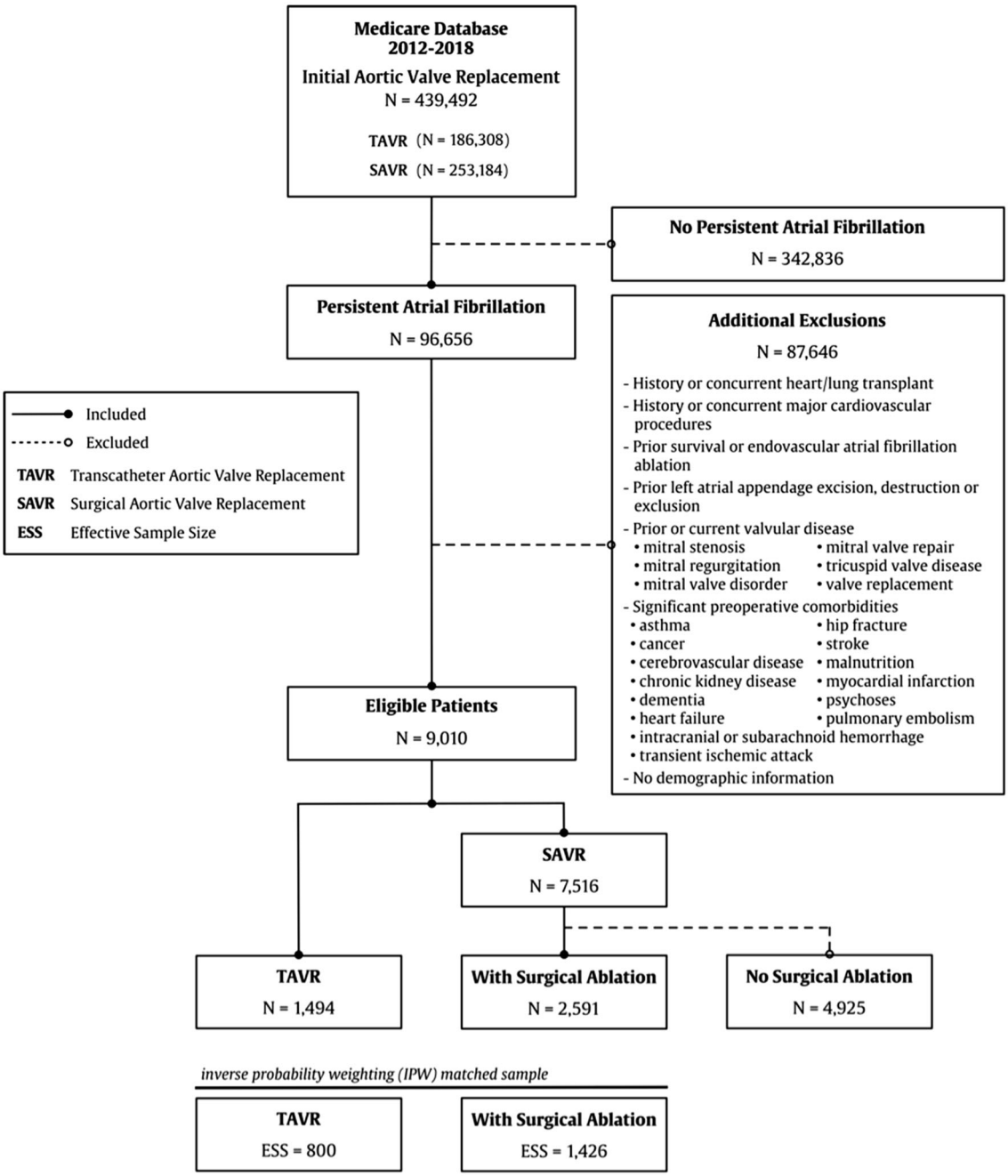


Fig. 1 CONSORT diagram showing selection of study sample. *TAVR* transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *SA* surgical ablation, *ESS* effective sample size. *Morbidities excluded asthma, chronic pulmonary disease, cancer, cerebrovascular disease, chronic kidney disease, dementia, heart failure, intracranial or subarachnoid hemorrhage, diabetes (complicated), transient ischemic attack, hip fracture, stroke, malnutrition, myocardial infarction, psychoses, pulmonary embolism, hypertension (complicated), liver disease, paralysis, emergent or urgent admission, blood loss anemia

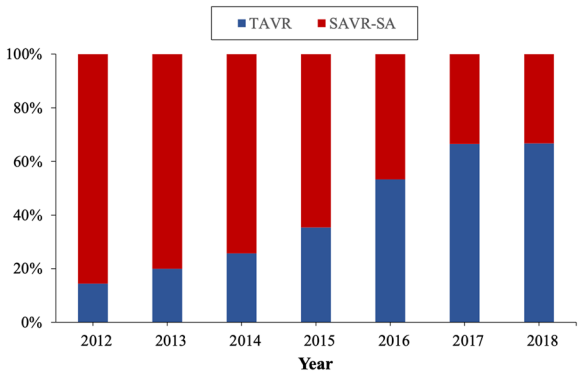


Fig. 2 Bar graphs depicting annual proportion of aortic valve replacements performed each year by procedure type. The proportion patients with atrial fibrillation who underwent SAVR-SA as opposed to TAVR alone steadily decreased from 86% in 2012 to 33% in 2018 (χ^2 (1, N = 4100) = 2854, $p < 0.01$)

Groups were adequately matched with respect to all baseline characteristics (Table 2). Analysis of propensity scores used to perform inverse probability of treatment weighting demonstrated adequate model performance (Supplementary Material Figs. 1–5). Patients who underwent SAVR-SA were on average 1.4 years younger with a CHA_2DS_2-VASc score 0.1 points lower than those undergoing TAVR alone; however, the standardized mean difference was 0.19 and 0.13, respectively, which meets criteria for acceptable balance. All other variables achieved ideal balance between groups, including HAS-BLED score.

All-cause mortality was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (30.3% vs. 52.3% at 5 years; adjusted hazard ratio (HR) 0.65, 95% confidence interval (CI) 0.53–0.79; $p < 0.01$) (Fig. 3, Table 3). CHA_2DS_2-VASc score was also an independent predictor of all-cause mortality (adjusted HR 1.39, 95% CI 1.18–1.65).

There was no significant difference in the incidence of transient ischemia attack between those who underwent SAVR-SA compared to TAVR alone (4.9% vs. 5.3% at 5 years; adjusted HR 1.05, 95% CI 0.75–1.47; $p = 0.79$) (Fig. 4a, Table 3). Similarly, there was no significant difference in the incidence of stroke between those who underwent SAVR-SA compared to TAVR alone (3.2% vs. 2.8% at 5 years; adjusted HR 1.07, 95% CI 0.74–1.54; $p = 0.72$) (Fig. 4b, Table 3).

The incidence of pacemaker implantation was significantly lower among those who underwent SAVR-SA compared to TAVR alone (8.6% vs. 14.6% at 5 years; adjusted HR 0.62, 95% CI 0.44–0.87; $p < 0.01$), with most incidences occurring in the early postoperative period for both groups (Fig. 4c, Table 3). The incidence of bleeding was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (4.8% vs. 6.7% at 5 years; adjusted HR 0.63, 95% CI 0.39–1.00; $p = 0.05$) (Fig. 4d, Table 3). The cumulative incidence of rehospitalization for atrial arrhythmias was lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (19.5% vs. 27.4% at 5 years). There was a significant difference between groups when compared using a log-rank test ($p = 0.02$), but there was no significant difference when compared using an adjusted Cox proportional-hazards model (adjusted HR 0.91, 95% CI 0.68–1.21; $p = 0.50$) (Fig. 4e, Table 3). Finally, rehospitalization for heart failure was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (10.8% vs. 24.9% at 5 years; adjusted HR 0.49, 95% CI 0.36–0.65; $p < 0.01$) (Fig. 4f, Table 3). Full results of the adjusted and unadjusted Cox proportional-hazard models for each outcome are provided (Supplementary Material Tables 2–8).

The falsification endpoint of rehospitalization for sepsis following the index procedure was not significantly different between those who underwent SAVR-SA compared to TAVR alone over a 5-year period (adjusted HR 1.13, 95% CI 0.82–1.55; $p = 0.45$; log-rank test, $p = 0.12$) (Supplementary Material Fig. 6, Table 9). The results did not change significantly between landmarked analysis at 180 days and non-landmarked analysis.

DISCUSSION

In this large, national study of Medicare beneficiaries with persistent, non-valvular AF undergoing aortic valve replacement, we demonstrate that select patients may:

Table 1 Unmatched baseline characteristics of sample population

Characteristic	TAVR (n = 1494)	SAVR-SA (n = 2591)	Total (n = 4085)	SMD or p value
Age, mean (SD)	83.6 (6.8)	75.7 (6.3)	78.6 (7.5)	1.22
Male, n (%)	776 (51.9)	1794 (69.3)	2570 (62.9)	0.36
Race, n (%)				0.02
Unknown	3 (0.2)	27 (1.0)	30 (0.7)	
White	1444 (96.7)	2488 (96.0)	3932 (96.3)	
Black	21 (1.4)	28 (1.1)	49 (1.2)	
Other	5 (0.3)	20 (0.8)	25 (0.6)	
Asian	10 (0.7)	10 (0.4)	20 (0.5)	
Hispanic	8 (0.5)	15 (0.6)	23 (0.6)	
Native American	3 (0.2)	3 (0.1)	6 (0.2)	
Year, n (%)				< 0.01
2012	84 (5.6)	499 (19.3)	583 (14.3)	
2013	133 (8.9)	534 (20.6)	667 (16.3)	
2014	211 (14.0)	611 (23.6)	822 (20.1)	
2015	243 (16.3)	444 (17.1)	687 (16.8)	
2016	235 (15.7)	207 (8.0)	442 (10.8)	
2017	282 (18.9)	141 (5.4)	423 (10.4)	
2018	306 (20.5)	155 (6.0)	461 (11.3)	
Preoperative comorbidities, mean (SD)				
CHA_2DS_2-VASC score	3.7 (0.9)	3.0 (1.0)	3.2 (1.0)	0.71
HAS-BLED score	1.9 (0.4)	1.8 (0.5)	1.9 (0.5)	0.16
Elixhauser comorbidities, n (%)				
Coagulopathy	115 (7.7)	232 (9.0)	347 (8.5)	− 0.05
Depression	105 (7.0)	182 (7.0)	287 (7.0)	0.00
Deficiency anemia	40 (2.7)	31 (1.2)	71 (1.7)	0.11
Diabetes, uncomplicated	364 (24.4)	605 (23.4)	969 (23.7)	0.02
Fluid and electrolyte disorders	134 (9.0)	197 (7.6)	331 (8.1)	0.05
Hypertension, uncomplicated	1281 (85.8)	2089 (80.6)	3370 (82.5)	0.14
Hypothyroidism	317 (21.2)	379 (14.6)	696 (17.0)	0.18
Other neurological disorders	57 (3.8)	78 (2.6)	125 (3.1)	0.07
Obesity	192 (12.9)	572 (22.1)	764 (18.7)	− 0.24
Pulmonary circulation disorders	198 (13.3)	268 (10.3)	466 (11.4)	0.09

Table 1 continued

Characteristic	TAVR (n = 1494)	SAVR-SA (n = 2591)	Total (n = 4085)	SMD or p value
Peripheral vascular disorders	277 (18.5)	524 (20.2)	801 (19.6)	− 0.04
Rheumatoid arthritis/collagen vascular	64 (4.3)	86 (3.3)	150 (3.7)	0.05
Peptic ulcer disease excluding bleeding	11 (0.7)	15 (0.6)	26 (0.6)	0.02
Weight loss	4 (0.3)	7 (0.3)	11 (0.3)	0.00

SMD standardized median difference (Cohen's *d*), *SD* standard deviation

1. Derive a survival benefit from SAVR-SA compared to TAVR alone.
2. Experience lower rates of pacemaker implantation, bleeding, and rehospitalization for heart failure following SAVR-SA compared to TAVR alone.

This study population was carefully selected for patients in whom equipoise likely remains between SAVR and TAVR and in whom the etiology of AF is homogenous. Patients with known high-risk characteristics for surgery, such as prior cardiac surgery, heart failure, pulmonary or renal disease, chronic obstructive pulmonary disease, and malnutrition, were excluded for the former reason. Patients with the possibility of having other valvular etiologies for AF were excluded for the latter reason. Some comorbidities such as peripheral vascular disorders and obesity were not excluded because of their high prevalence in both treatment groups. We selected patients with persistent AF because they have worse long-term outcomes compared to those with paroxysmal AF and may therefore benefit most from restoration of atrioventricular synchrony. Additionally, the treatment of persistent AF via catheter ablation can be challenging and is less efficacious than a complete surgical lesion set [22].

We found SAVR-SA to be associated with a 35% reduction in the risk of all-cause mortality. Initially those who underwent SAVR-SA incurred a higher rate of mortality; however, 6–12 months following the operation, they were surpassed by the cumulative incidence of mortality in the those who underwent TAVR alone. In the report of 5-year outcomes of the PARTNER II trial the cumulative incidence of death or disabling stroke in patients who underwent TAVR crossed above those who underwent SAVR around 36 months following the procedure [23]. There has been debate whether the addition of SA to SAVR increases short-term morbidity or mortality; however, recent compelling evidence suggests that it does not, particularly in isolated SAVR [4, 8, 11, 24]. Our patient population was older than the average patient included in these studies by roughly 5–10 years, and this early mortality may be evidence that we captured an above-average risk cohort undergoing SAVR. This would bias our conclusion towards the null. The long-term mortality benefit for SAVR-SA demonstrated in this study is evident, has a strong pathophysiological basis, and is consistent with prior studies [2, 11, 25].

We did not find a significant difference in the rate of cerebrovascular events, either stroke or transient ischemic attack, between groups. The incidence of cerebrovascular events in both treatment groups was lower than that reported in the 5-year follow-up of the PARTNER II trial. This could be due to poor capture within claims data, which is estimated to have a sensitivity of around 60% for stroke [26]. Evidence for the efficacy of concomitant SA for the long-term reduction of cerebrovascular events is mixed—

Table 2 Matched baseline characteristics of sample population

Characteristic	TAVR (ESS = 800)	SAVR-SA (ESS = 1426)	Total (ESS = 2075)	SMD
Age, mean (SD)	79.3 (7.4)	77.9 (7.2)	78.6 (7.3)	0.19
Male, SOW (% weight)	411 (51.4)	1053 (73.8)	1229 (59.2)	0.06
Preoperative comorbidities, mean (SD)				
CHA_2DS_2-VASC score	3.3 (1.0)	3.2 (1.0)	3.2 (1.0)	0.13
HAS-BLED score	1.9 (0.5)	1.9 (0.5)	1.9 (0.5)	0.01
Preoperative comorbidities, SOW (% weight)				
Coagulopathy	68 (8.5)	182 (12.8)	205 (9.9)	− 0.01
Depression	62 (7.7)	142 (10.0)	176 (8.5)	− 0.01
Deficiency anemia	37 (4.6)	25 (1.7)	60 (2.9)	0.03
Diabetes, uncomplicated	236 (29.4)	479 (33.6)	639 (30.8)	0.00
Fluid and electrolyte disorders	68 (8.4)	152 (10.7)	179 (8.6)	0.05
Hypertension, uncomplicated	683 (85.3)	1082 (75.9)	1690 (81.5)	0.00
Hypothyroidism	177 (22.2)	218 (15.3)	389 (18.7)	0.05
Other neurological disorders	38 (4.8)	55 (3.9)	89 (4.3)	0.02
Obesity	116 (14.5)	483 (33.9)	406 (19.6)	− 0.05
Pulmonary circulation disorders	92 (11.5)	208 (14.6)	242 (11.7)	0.06
Peripheral vascular disorders	157 (19.7)	195 (13.7)	352 (17.0)	− 0.09
Rheumatoid arthritis/collagen vascular	48 (6.0)	70 (4.9)	113 (5.4)	0.02
Peptic ulcer disease excluding bleeding	8 (1.0)	14 (1.0)	20 (0.9)	0.01
Weight loss	4 (0.5)	7 (0.5)	11 (0.5)	− 0.02

ESS effective sample size, *SMD* standardized mean difference, *SD* standard deviation, *SOW* sum of weights

some studies demonstrate a reduction but most do not [12, 20, 27, 28].

We found the utilization of SAVR-SA to be associated with a 38% reduction in rate of pacemaker implantation. This came almost exclusively in the early postoperative period. The association between TAVR and conduction abnormalities requiring pacemaker implantation is well known and this finding is not surprising. The incidence of pacemaker implantation at 5 years in this study (15%) is nearly identical to that reported in the 5-year follow-up of the PARTNER II trial (16%) [23]. Curiously, the incidence of pacemaker implantation among those who underwent SAVR-SA (9%) was lower than that reported for SAVR in the 5-year follow-up of the PARTNER II trial (13%), despite the conventional wisdom that SA may unmask sinus node dysfunction associated with AF.

Utilization of SAVR-SA was associated with a 37% reduction in risk of bleeding, 51% reduction in risk of rehospitalization for heart failure, and 9% reduction in risk of rehospitalization for

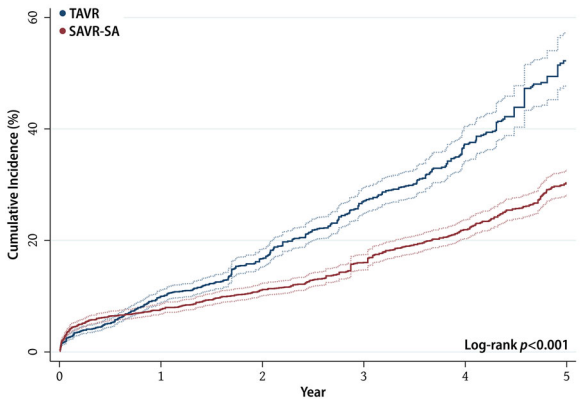


Fig. 3 Cumulative all-cause mortality following aortic valve replacement stratified by procedure. All-cause mortality was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (30.3% vs. 52.3% at 5 years; adjusted HR 0.65, 95% CI 0.53–0.79; $p < 0.01$)

atrial arrhythmias. The pattern of late divergence seen in the cumulative incidence plot for rehospitalization for atrial arrhythmias, as well as significant difference when procedures were compared using a log-rank test, suggests there may be a true late effect. This finding is consistent with other reports [6, 20]. The lower incidence of bleeding may be due to reduction in anticoagulant utilization in patients who underwent SAVR-SA, but this cannot be determined from our dataset. The decision to landmark rehospitalization for both atrial arrhythmias and heart failure is based on data that suggests early rehospitalization after SAVR is not associated with poor long-term outcomes [29]. Reduction in rehospitalization, at any time, is likely to improve patient quality of life and may contribute to the long-term cost-effectiveness of SAVR-SA [20].

Approximately 35% (2591/7516) of eligible patients in this sample underwent concomitant SA. This is slightly lower than previous reports from another national sample and in part reflects a reluctance among surgeons to perform concomitant SA. More importantly, we show that the proportion of patients with persistent AF undergoing TAVR alone rather than SAVR-SA has dramatically increased. This implies that the importance of replacement approach has potentially superseded the importance of restoring atrioventricular synchrony in the complex decision-making process regarding utilization of SAVR versus TAVR. However, given these results, does the importance of restoring atrioventricular synchrony warrant more weight in determining which procedure to recommend to low- and intermediate-risk patients?

Our weighted study population is most similar to an intermediate-risk population as defined in the PARTNER II trial. This is expected because TAVR had not yet achieved an indication in low-risk patients during this study period and because factors for AF include age and comorbidities such as chronic obstructive pulmonary disease, hypertension, renal dysfunction, and diabetes. Our average patient was 78 and 79 years old in the SAVR-SA and TAVR alone groups, respectively, which compares favorably with the average age of participants in the PARTNER II trial, who were 82 years old on average [30]. Though we were unable to determine surgical risk as precisely as the PARTNER II trial, we insured against this by taking a highly restrictive approach towards comorbidities. It is reassuring that the 5-year mortality rate for TAVR in this study (52%) is similar to that observed in the 5-year follow-up of the PARTNERS II trial (46%) [23]. The 6% difference can be reasonably explained by the fourfold increased risk of mortality documented in patients with AF, a risk that may be even higher in those with AF not treated during valve replacement [11, 17, 31–33].

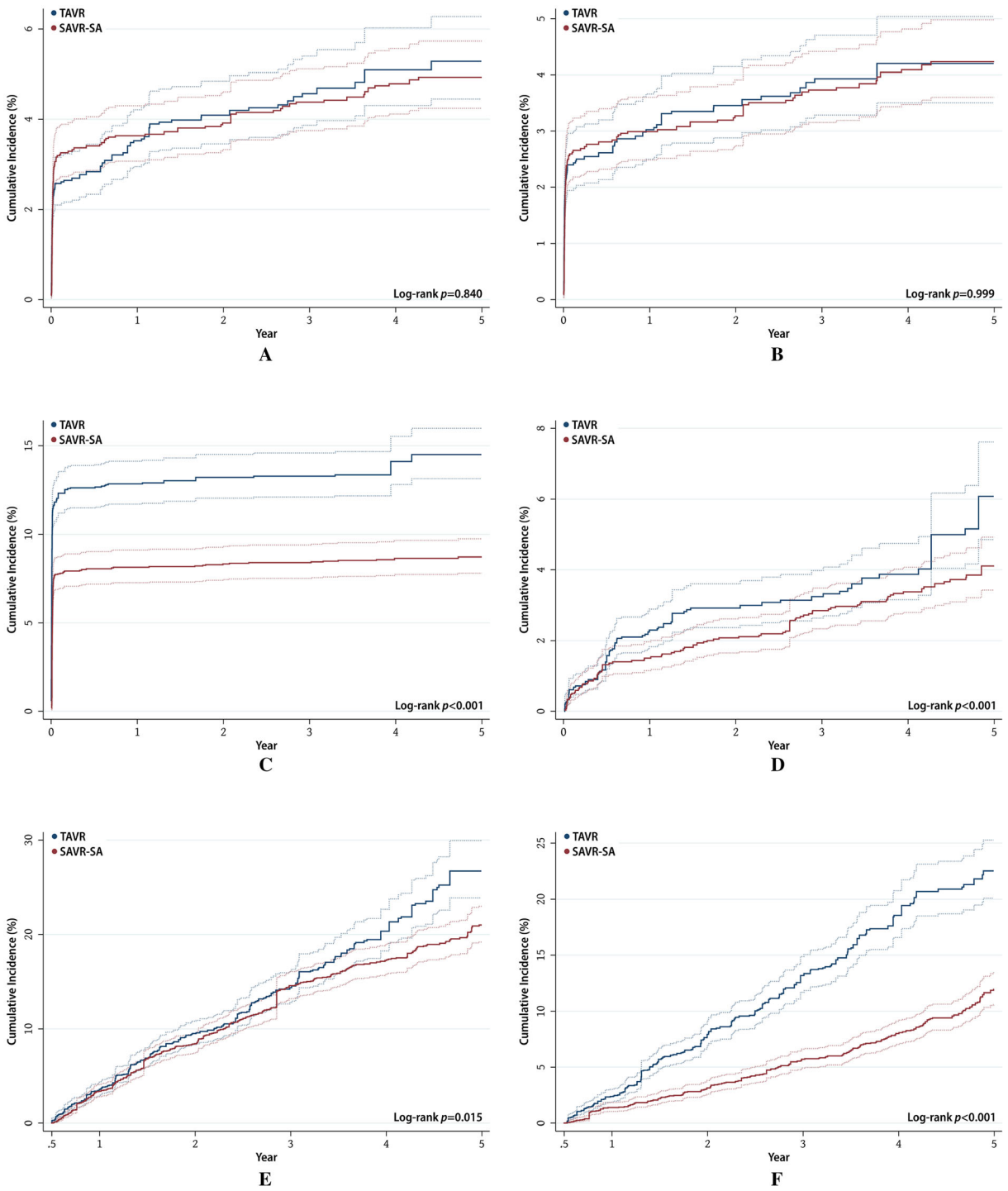
This study has important limitations in addition to the ones already discussed. It is

Table 3 Summary of primary and secondary outcomes

Outcome	Cumulative incidence at 5-years % (95% CI)[a]		Hazard ratio (95% CI)[a]				log-rank test
	TAVR	SAVR-SA	Matched Cox proportional-hazards model	*p* value	Matched Cox proportional-hazards model with multivariable regression	*p* value	*p* value
All-cause mortality	52.3 (47.7–57.3)	30.3 (28.2–32.7)	0.61 (0.50–0.73)	< 0.01	0.65 (0.53–0.79)	< 0.01	< 0.01
Transient ischemic attack	5.3 (4.5–6.3)	4.9 (4.2–5.7)	0.98 (0.70–1.36)	0.89	1.05 (0.75–1.47)	0.79	0.84
Stroke	2.8 (2.2–3.6)	3.2 (2.7–3.9)	1.00 (0.70–1.43)	1.00	1.07 (0.74–1.54)	0.72	1.00
Pacemaker implantation	14.6 (13.3–16.0)	8.6 (7.7–9.6)	0.60 (0.44–0.83)	< 0.01	0.62 (0.44–0.87)	< 0.01	< 0.01
Bleeding	6.7 (5.5–8.1)	4.8 (4.1–5.6)	0.61 (0.39–0.96)	0.03	0.63 (0.39–1.00)	0.05	< 0.01
Rehospitalization for atrial arrhythmia[b]	27.4 (24.4–30.9)	19.5 (17.7–21.4)	0.85 (0.65–1.11)	0.24	0.91 (0.68–1.21)	0.50	0.02
Rehospitalization for heart failure[b]	24.9 (22.2–27.9)	10.8 (9.5–12.3)	0.47 (0.35–0.62)	< 0.01	0.49 (0.36–0.65)	< 0.01	< 0.01

[a]For SAVR with SA compared to TAVR alone
[b]Landmarked at 180 days

reliant on Medicare claims data, which is subject to coding error and does not capture important baseline characteristics such as frailty and echocardiographic data. This registry also lacks details such as cause of death, severity of stroke or bleed, and use of antiarrhythmic or anticoagulant medications. Furthermore, it is not possible to determine the technical details of the valve replacement (e.g., manufacturer, size, and approach) or of the SA (e.g., energy source and lesion set). Although a Cox-Maze IV procedure is the gold standard for SA, it is often not performed for a variety of reasons. Use of suboptimal lesions sets, particularly in a population with persistent AF, would bias our conclusions towards the null. Lastly, although we used rigorous weighting methodology to account for confounding, this methodology cannot account for confounding owing to unmeasured variables. In particular, confounding by indication and patient or provider preference is a significant concern in this population. Because rehospitalization for sepsis 180 days or more beyond the procedure is unlikely to associated with the procedure but is likely to be associated with overall health status of the patient, it can serve as a falsification endpoint. There was no difference in the incidence of rehospitalization for sepsis between those who underwent SAVR-SA compared to


TAVR
SAVR-SA
Cumulative Incidence (%)
Year
Log-rank p=0.840
A
Log-rank p=0.999
B
Log-rank p<0.001
C
Log-rank p<0.001
D
Log-rank p=0.015
E
Log-rank p<0.001
F

◀**Fig. 4** Cumulative incidence of secondary outcomes with death as a competing risk stratified by procedure type. **a** Transient ischemic attack. There was no significant difference in the incidence of transient ischemia attack between those who underwent SAVR-SA compared to TAVR alone (3.6% vs. 3.5% at 5 years; adjusted HR 1.05, 95% CI 0.75–1.47; $p = 0.79$). **b** Stroke. There was no significant difference in the incidence of stroke between those who underwent SAVR-SA compared to TAVR alone (3.2% vs. 2.8% at 5 years; adjusted HR 1.07, 95% CI 0.74–1.54; $p = 0.72$) **c** Pacemaker implantation. There was significantly lower incidence of pacemaker implantation among those who underwent SAVR-SA compared to TAVR alone (8.6% vs. 14.6% at 5 years; adjusted HR 0.62, 95% CI 0.44–0.87; $p < 0.01$), with most incidences occurring in the early postoperative period for both groups. **d** Bleeding. The incidence of bleeding was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (4.8% vs. 6.7% at 5 years; adjusted HR 0.63, 95% CI 0.39–1.00; $p = 0.05$). **e** Rehospitalization for an atrial arrhythmia (landmarked at 180 days). The cumulative incidence of rehospitalization for atrial arrhythmias was lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (19.5% vs. 27.4% at 5 years). There was a significant difference between groups when compared using a log-rank test ($p = 0.02$), but there was no significant difference when compared using an adjusted Cox proportional-hazards model (adjusted HR 0.91, 95% CI 0.68–1.21; $p = 0.50$). **f** Rehospitalization for heart failure (landmarked at 180 days). The incidence of rehospitalization for heart failure was significantly lower for patients who underwent SAVR-SA compared to those who underwent TAVR alone (10.8% vs. 24.9% at 5 years; adjusted HR 0.49, 95% CI 0.36–0.65; $p < 0.01$)

TAVR alone. This provides a measure of assurance that the strict inclusion criteria as well as rigorous weighting technique adequately mitigated the effect of unmeasured confounding.

In conclusion, this study demonstrates for the first time that select patients undergoing aortic valve replacement with persistent non-valvular AF may derive significant benefit from SAVR-SA compared to TAVR alone with respect to mortality, pacemaker implantation, bleeding, and rehospitalization. This evidence questions the appropriateness of the trendy use of TAVR among a population of patients with a surgically modifiable risk factor for long-term mortality and morbidity.

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Compliance with Ethics Guidelines. This project (protocol number 849385) was reviewed the IRB at the University of Pennsylvania and deemed exempt from approval according to 45 CFR 46.104, category 4. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the United States

government Centers for Medicare & Medicaid Services. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the Centers for Medicare & Medicaid Services upon request and approval.

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