

Postoperative Atrial Fibrillation or Flutter Following Transcatheter or Surgical Aortic Valve Replacement



PARTNER 3 Trial

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ABSTRACT

OBJECTIVES The aim of this study was to assess the incidence and prognostic impact of early and late postoperative atrial fibrillation or flutter (POAF) in patients with severe aortic stenosis (AS) treated with transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR).

BACKGROUND There is an ongoing controversy regarding the incidence, recurrence rate, and prognostic impact of early (in-hospital) POAF and late (postdischarge) POAF in patients with AS undergoing TAVR or SAVR.

METHODS In the PARTNER (Placement of Aortic Transcatheter Valve) 3 trial, patients with severe AS at low surgical risk were randomized to TAVR or SAVR. Analyses were performed in the as-treated population excluding patients with preexistent atrial fibrillation or flutter.

RESULTS Among 781 patients included in the analysis, early POAF occurred in 152 (19.5%) (18 of 415 [4.3%] and 134 of 366 [36.6%] following TAVR and SAVR, respectively). Following discharge, 58 new or recurrent late POAF events occurred within 1 year following the index procedure in 55 of 781 patients (7.0%). Early POAF was not an independent predictor of late POAF following discharge (odds ratio: 1.04; 95% CI: 0.52-2.08; $P = 0.90$). Following adjustment, early POAF was not an independent predictor of the composite outcome of death, stroke, or rehospitalization (hazard ratio: 1.10; 95% CI: 0.64-1.92; $P = 0.72$), whereas late POAF was associated with an increased adjusted risk for the composite outcome (hazard ratio: 8.90; 95% CI: 5.02-15.74; $P < 0.0001$), irrespective of treatment modality.

CONCLUSIONS In the PARTNER 3 trial, early POAF was more frequent following SAVR compared with TAVR. Late POAF, but not early POAF, was significantly associated with worse outcomes at 2 years, irrespective of treatment modality. (J Am Coll Cardiol Intv 2021;14:1565-74) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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**ABBREVIATIONS
AND ACRONYMS****AF** = atrial fibrillation or flutter**AS** = aortic stenosis**HR** = hazard ratio**LAV** = left atrial volume**LVEF** = left ventricular ejection fraction**POAF** = postoperative atrial fibrillation or flutter**SAVR** = surgical aortic valve replacement**TAVR** = transcatheter aortic valve replacement

Postoperative atrial fibrillation or flutter (POAF) is a common complication in patients undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for severe aortic stenosis (AS) (1-14). Prior studies have largely focused on early POAF occurring during the index hospitalization following SAVR or TAVR, and the reported incidence and clinical impact of early POAF have varied significantly across studies, likely because of limitations related to small sample sizes and lack of randomization (15,16). As such, there are limited data on occurrence or recurrence of POAF following

discharge from the index hospitalization. Accordingly, the association between early (in-hospital) and late (postdischarge) POAF following TAVR or SAVR for severe AS has not been thoroughly investigated. Furthermore, POAF following TAVR or SAVR has been studied largely within the context of patients at intermediate or high surgical risk, and the incidence and prognostic impact of atrial fibrillation or flutter (AF) following TAVR or SAVR in patients with AS at low surgical risk remain unknown. In the present analysis of the PARTNER (Placement of Aortic Transcatheter Valve) 3 trial, we sought to determine the incidence and prognostic impact of POAF according to timing of occurrence and the association between early in-hospital and late (postdischarge) POAF in patients with severe AS at low surgical risk who underwent TAVR or SAVR.

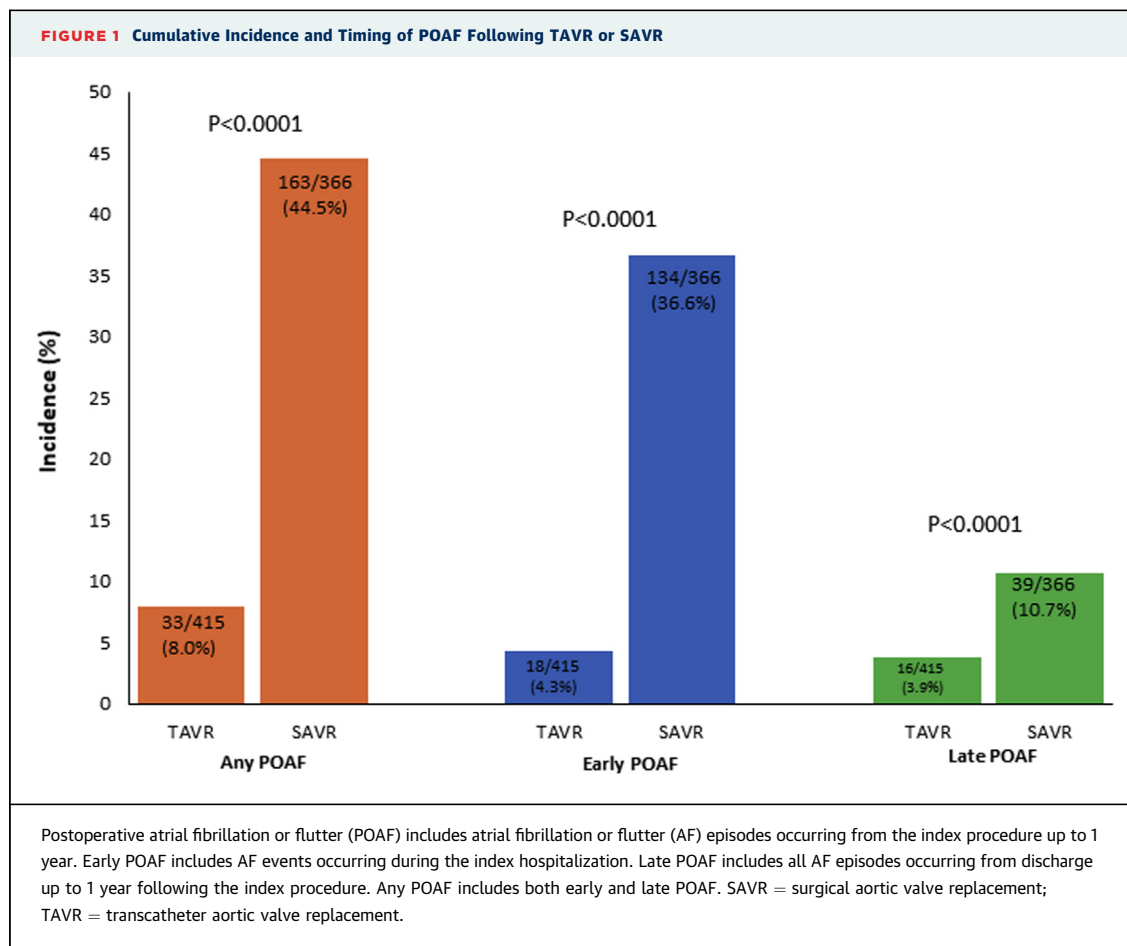
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METHODS

STUDY DESIGN AND ENDPOINTS. The design and primary results of the PARTNER 3 trial have been reported previously (17). In brief, the PARTNER 3 trial was a multicenter, randomized trial in which TAVR with transfemoral placement of a third-generation balloon-expandable valve was compared with standard SAVR in patients with severe AS and a low risk for death with surgery. Patients were eligible for inclusion if they had severe calcific AS and were considered to be at low surgical risk according to the results of clinical and anatomic assessment, including a Society of Thoracic Surgeons Predicted Risk of Mortality score of <4% and agreement by the site heart team and the trial case review committee. Details regarding inclusion and exclusion criteria have previously been reported (17). Eligible patients were randomly assigned, in a 1:1 ratio, to undergo either TAVR with the SAPIEN 3 system (Edwards Lifesciences) or SAVR with a commercially available bioprosthetic valve. The investigation was approved by the

Institutional Review Board or ethics committee at each participating center, and all patients provided written informed consent. Major endpoints were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation). The primary endpoint was a composite of death of any cause, stroke, or rehospitalization at 1 year after the procedure. For the purpose of the present study, the primary endpoint was defined a priori as the composite outcome of death of any cause, stroke, or rehospitalization at 2 years. Secondary endpoints included the individual endpoints of rehospitalization for procedure- or device-related adverse events or heart failure, as well as all-cause death, cardiovascular death, stroke, and major bleeding, including major bleeding and life-threatening bleeding per the Valve Academic Research Consortium-2 definition. Major endpoints and arrhythmic events, including AF, were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation). For the purpose of the present study, POAF was categorized into 3 groups: early POAF, including any AF occurring during the index hospitalization pre-discharge; late POAF, including any AF occurring after hospital discharge up to 1 year; and any POAF, including both early and late POAF. Clinical follow-up is presently complete for all patients through 2 years. Median follow-up duration for clinical outcomes was 2.07 years (interquartile range: 2.01 years-2.45 years).

STATISTICAL METHODS. In the present study, all arrhythmic events reported and adjudicated as POAF and occurring at any time following the index TAVR or SAVR procedure and up to 1 year were analyzed. Analyses were performed in the as-treated population, excluding patients with preexisting AF and those in whom no aortic valve replacement was performed. Main analyses were based on early POAF; alternative analyses were performed for any and late POAF. Continuous variables are reported as mean \pm SD and were compared using Student's *t*-test. Categorical variables are expressed as counts and percentages and were compared with the chi-square or Fisher exact test, as appropriate. Predictors of early, late, and any POAF were determined in a logistic regression model including the following clinically pertinent variables: age, sex, history of diabetes, history of hypertension, history of congestive heart failure, history of stroke or transient ischemic attack, body mass index, baseline hemoglobin, creatinine clearance, left ventricular ejection fraction (LVEF), left atrial volume (LAV), and treatment modality (TAVR or SAVR). Furthermore, an alternative model including the aforementioned covariates as well as early POAF was constructed for prediction of late POAF. Rates of adverse clinical outcomes were estimated using the Kaplan-Meier method and compared



using the log-rank test. The adjusted association between early, late, and any POAF and adverse clinical outcomes was assessed using multivariable Cox proportional hazards regression, including the following covariates: age, sex, history of diabetes, history of hypertension, history of congestive heart failure, history of stroke or transient ischemic attack, body mass index, baseline hemoglobin, creatinine clearance, LVEF, and treatment modality (TAVR or SAVR) as well as POAF modeled as a time-updated variable (18). Secondary models were constructed including anticoagulant therapy at discharge. A 2-sided P value < 0.05 was considered to indicate statistical significance for all tests. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

INCIDENCE, TIMING, AND RECURRENCE RATE OF AF. Among 781 patients included in the present analysis, 366 (46.9%) underwent SAVR and 415 (53.1%) underwent TAVR. Overall rates of any POAF, early POAF, and late POAF according to treatment

modality are shown in [Figure 1](#) and [Supplemental Figure 1](#). Early POAF occurred in 152 of 781 patients (19.5%) (18 of 415 [4.3%] after TAVR and 134 of 366 [36.6%] after SAVR; $P < 0.0001$) at a mean of 2.34 ± 1.81 days following the index procedure. By hospital discharge, early POAF had resolved in 109 of 131 patients (83.2%) (14 of 15 [93.3%] of those in the TAVR arm and 95 of 116 [81.9%] of those in the SAVR arm), of whom 20 patients underwent direct-current cardioversion and 88 patients received rhythm and/or rate control medical therapies. Following discharge, 58 late POAF events (new or recurrent) occurred during 1-year follow-up in 55 of 781 patients (7.0%) (39 of 366 [10.4%] following SAVR vs 16 of 415 [3.8%] following TAVR; $P < 0.0001$); of these, 24 episodes (44.4%) occurred within 30 days of the index procedure. The median time to AF recurrence after a first event was 43.5 days (interquartile range: 8 days–133 days). Recurrent AF after discharge occurred in 13 of 152 patients (8.6%) with early POAF, whereas 42 of 629 patients (6.7%) without early POAF developed late POAF ($P = 0.48$). Collectively, within 1 year of the index procedure, any POAF was detected in

TABLE 1 Baseline Characteristics of Patients With Versus Without Early POAF

	Early POAF (n = 152)	No Early POAF (n = 629)	P Value
Age, y	74.7 ± 5.7	73.0 ± 6.0	0.001
Male	103/152 (67.8)	420/629 (66.8)	0.85
Nonwhite race or ethnic group	15/152 (9.9)	60/629 (9.5)	0.88
Body mass index, kg/m ²	30.4 ± 5.1	30.3 ± 5.3	0.70
STS score	2.0 ± 0.6	1.9 ± 0.7	0.06
EuroSCORE II	1.5 ± 1.0	1.5 ± 1.2	0.84
NYHA functional class III or IV	38/152 (25.0)	171/629 (27.2)	0.61
CHA ₂ DS ₂ -VASc score	3.6 ± 1.3	3.5 ± 1.2	0.37
Coronary artery disease	46/152 (30.3)	169/628 (26.9)	0.42
Previous myocardial infarction	8/152 (5.3)	32/626 (5.1)	1.00
Previous stroke or cerebrovascular accident	7/152 (4.6)	24/628 (3.8)	0.65
Carotid disease	17/148 (11.5)	75/614 (12.2)	0.89
Peripheral vascular disease	7/152 (4.6)	49/627 (7.8)	0.22
Chronic obstructive pulmonary disease	5/152 (3.3)	39/628 (6.2)	0.24
Creatinine >2 mg/dL	1/152 (0.7)	1/629 (0.2)	0.35
Diabetes mellitus	42/151 (27.8)	194/629 (30.8)	0.49
Pulmonary hypertension	8/152 (5.3)	27/628 (4.3)	0.66
Hyperlipidemia	123/152 (80.9)	508/629 (80.8)	1.00
Hypertension	129/152 (84.9)	533/628 (84.9)	1.00
Congestive heart failure	53/152 (34.9)	218/628 (34.7)	1.00
Pulmonary disease	9/152 (5.9)	33/628 (5.3)	0.69
PCI or CABG	28/152 (18.4)	116/627 (18.5)	1.00
Anemia	10/152 (6.6)	51/629 (8.1)	0.62
Renal disease	16/152 (10.5)	64/629 (10.2)	0.88
History of alcohol abuse	11/152 (7.2)	50/629 (7.9)	0.87
History of cancer	31/152 (20.4)	150/626 (24.0)	0.39
History of tobacco use	81/152 (53.3)	333/629 (52.9)	1.00

Values are mean ± SD or n/N (%).

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; POAF = postoperative atrial fibrillation or flutter; STS = Society of Thoracic Surgeons.

196 patients (12.3%) (163 of 366 [44.5%] following SAVR and 33 of 415 [8.0%] following TAVR; $P < 0.0001$). Among all patients with any POAF following SAVR, 146 (89.6%) had a single episode, 15 (9.2%) had 2 episodes, and 2 (1.2%) had ≥ 3 episodes, whereas among all patients following TAVR, 30 patients (90.9%) had a single AF episode and 3 (9.1%) had 2 AF episodes.

BASELINE, ECHOCARDIOGRAPHIC, AND PROCEDURAL CHARACTERISTICS. Baseline, echocardiographic, and procedural characteristics of patients with or without early POAF are shown in [Tables 1, 2, and 3](#), respectively. Compared with patients without early POAF, patients with early POAF were older ([Table 1](#)), had higher LVEFs ([Table 2](#)), and had longer procedural time and hospital stay ([Table 3](#)). At discharge, 51.3% of

patients with early POAF were on anticoagulant medications compared with 16.1% of patients without early POAF ([Table 4](#)). Baseline, echocardiographic, and procedural characteristics of patients with versus without early POAF were overall similar within the TAVR and SAVR arms ([Supplemental Tables 1 to 4](#)). Patients with early POAF undergoing SAVR were older and had higher Society of Thoracic Surgeons risk scores. Among patients undergoing TAVR, more than 1 postdilatation was more frequently performed in patients with early POAF compared with those without early POAF. Clinical characteristics, anticoagulant agent use, and echocardiographic and procedural characteristics according to late POAF or any POAF are shown in [Supplemental Tables 5 to 8](#). Patients with any POAF as well as those with late POAF had larger LAV and longer procedural times and index hospital stays.

PREDICTORS. Age, LAV, and SAVR were independently associated with an increased risk for early POAF ([Supplemental Table 9](#)). Furthermore, age, LAV, and SAVR were independent predictors of any POAF, while LAV and SAVR were the only predictors of late POAF ([Supplemental Table 9](#)). Early POAF was not independently associated with the risk for late POAF (odds ratio: 0.96; 95% confidence interval [CI]: 0.48-1.94; $P = 0.92$).

CLINICAL OUTCOMES. Early POAF was associated with increased unadjusted rates of the composite outcome of death of any cause, stroke, or rehospitalization at 30 days, as well as stroke and bleeding; however, at 2 years, early POAF was no longer associated with increased unadjusted rates of stroke and the composite outcome ([Table 5](#)). Following adjustment, early POAF was not an independent predictor of 2-year adverse outcomes ([Table 6](#), [Central Illustration](#), top). In contrast, in alternative models including all or late POAF as time-updated covariates, both POAF occurring at any time following the procedure and up to 1 year and late POAF were independently associated with increased risk for the primary composite endpoint of death, stroke, or rehospitalization as well as the individual endpoints of stroke and rehospitalization ([Table 6](#), [Central Illustration](#), top). There was no interaction between treatment modality and early, late, or any POAF on the risk for the primary composite endpoint ($P_{\text{int}} = 0.31$, $P_{\text{int}} = 0.11$, and $P_{\text{int}} = 0.75$, respectively) ([Central Illustration](#), bottom). In additional alternative models including adjustment for anticoagulant therapy at discharge, late POAF and any POAF remained significant predictors of the primary composite endpoint of death, stroke, or rehospitalization

(hazard ratio [HR]: 9.20; 95% CI: 5.18-16.35; $P < 0.0001$; and HR: 2.44; 95% CI: 1.47-4.03; $P = 0.0005$) and the individual endpoint of rehospitalization (HR: 11.20; 95% CI: 5.85-21.44; $P < 0.0001$; and HR: 2.84; 95% CI: 1.59-5.05; $P = 0.0004$) (Supplemental Table 10). Late POAF, but not early or any POAF, was independently associated with an increased adjusted risk for death (HR: 5.10; 95% CI: 1.36-19.18; $P = 0.02$) and stroke (HR: 12.05; 95% CI: 3.1-47.1, $P = 0.0003$) (Supplemental Table 10).

Among patients with early POAF, 7 patients had strokes during follow-up; of those, 3 (42.9%) were being treated with anticoagulant therapy prior to the stroke and 4 of 7 (57.1%) were not ($P = 1.00$). Among patients with late POAF, 5 of 55 (9.1%) had strokes, and all were being treated with anticoagulant therapy prior to the stroke ($P = 0.008$). Overall, among patients with any POAF within 1 year from the index procedure, 10 of 196 (5.1%) had strokes; of those, 6 of 10 (60%) were on anticoagulant therapy prior to the event ($P = 0.66$).

DISCUSSION

In the present analysis from the PARTNER 3 trial, in which patients with severe AS at low surgical risk were randomized to TAVR or SAVR, we found that 1) early POAF occurred in 19.5% of included patients and was more common following SAVR; 2) the incidence of any POAF within 1 year following the index procedure was higher following SAVR compared with TAVR; 3) early POAF was not an independent predictor of late POAF; and 4) late POAF, but not early POAF, was independently associated with an increased unadjusted and adjusted risk for the composite outcome of all-cause death, stroke, or rehospitalization, irrespective of treatment modality.

To the best of our knowledge, the present study is the first to assess the time course of development of POAF following TAVR or SAVR in patients with severe AS at low surgical risk; furthermore, the present study addressed the association of early POAF with subsequent AF following discharge as well as the prognostic impact of POAF according to timing. Importantly, in the PARTNER 3 trial, all clinical or monitored AF events occurring within 1 year following the index procedure were independently adjudicated, thus allowing a unique opportunity to determine both early periprocedural as well as late clinical AF occurrence. Prior studies have reported a wide range of early POAF incidence following surgical or transcatheter therapies for severe AS, varying from 31% to 64% after SAVR (6) and from 1%-16% after transfemoral TAVR (8), mainly among patients at

TABLE 2 Baseline Echocardiographic and Computed Tomographic Characteristics of Patients With Versus Without Early POAF

	Early POAF (n = 152)	No Early POAF (n = 629)	P Value
Aortic valve area, cm ²	0.8 ± 0.2	0.8 ± 0.2	0.90
Aortic valve mean gradient, mm Hg	48.9 ± 11.6	49.2 ± 12.7	0.76
Left ventricular ejection fraction, %	67.7 ± 8.4	66.0 ± 8.9	0.03
Left atrial volume, mL	72.3 ± 21.8	68.0 ± 20.5	0.03
Peak pulmonary artery systolic pressure, mm Hg	34.8 ± 9.1	36.1 ± 9.4	0.24
Moderate or severe regurgitation			
Aortic	2/148 (1.4)	22/616 (3.6)	0.20
Mitral	4/147 (2.7)	8/603 (1.3)	0.26
Tricuspid	3/143 (2.1)	6/598 (1.0)	0.39
Computed tomography			
Systolic annular perimeter, mm	78.2 ± 6.9	77.7 ± 6.9	0.45
Systolic annular area, mm ²	475.5 ± 84.0	469.3 ± 83.4	0.42

Values are mean ± SD or n/N (%).
POAF = postoperative atrial fibrillation or flutter.

intermediate or high surgical risk. This wide variation in reported early POAF incidence is likely explained by differences in patient demographics, rhythm-monitoring techniques, AF diagnostic criteria, and procedure-related factors. Results from the present study reaffirm that early POAF remains a common phenomenon following SAVR, occurring in 36.6% of patients despite the lower risk population enrolled in PARTNER 3; similarly, early POAF was infrequent (4.3%) after TAVR but still within the range of previous findings (19,20). As such, the fact that early POAF was as prevalent as in higher risk patient cohorts underlines the pervasive significance of this arrhythmic phenomenon as well as at least its partial mediation through procedure-related factors, including postoperative inflammation, enhanced sympathetic stimulation, and oxidative stress (16), which come into play shortly after intervention but

TABLE 3 Procedural Characteristics of Patients With Versus Without Early POAF

	Early POAF (n = 152)	No Early POAF (n = 629)	P Value
Procedure time, min	185.0 (149.5-232.0)	74.0 (44.0-177.0)	<0.0001
Anesthesia type			<0.0001
General	138/152 (90.8)	367/629 (58.3)	
Conscious sedation	14/152 (9.2)	256/629 (40.7)	
Anesthesia time, min	286.5 ± 86.0	199.6 ± 102.4	<0.0001
Concomitant procedures	33/152 (21.7)	69/629 (11.0)	<0.001
Left atrial appendage ligation	5/152 (3.3)	7/629 (1.1)	0.07
Duration of hospital stay, d	7.0 (6.0-9.0)	3.0 (2.0-6.0)	<0.0001

Values are median (interquartile range), n/N (%), or mean ± SD.
POAF = postoperative atrial fibrillation or flutter.

TABLE 4 Anticoagulant and Antiplatelet Medications at Baseline and Follow-Up in Patients With Versus Without Early POAF

	Early POAF (n = 152)	No Early POAF (n = 629)	P Value
Baseline			
Anticoagulant medications	37/152 (24.3)	124/629 (19.7)	0.22
Antiplatelet medications	104/152 (68.4)	500/629 (79.5)	0.005
Discharge			
Anticoagulant medications	78/152 (51.3)	101/629 (16.1)	<0.0001
Antiplatelet medications	141/152 (92.8)	602/629 (95.7)	0.14
1 y			
Anticoagulant medications	34/152 (22.4)	46/629 (7.3)	<0.0001
Antiplatelet medications	131/152 (86.2)	573/629 (91.1)	0.09
2 y			
Anticoagulant medications	31/152 (20.4)	46/629 (7.3)	<0.001
Antiplatelet medications	122/152 (80.3)	532/629 (84.6)	0.22
Values are n/N (%).			
POAF = postoperative atrial fibrillation or flutter.			

subside within weeks. This hypothesis is further supported by our findings on late POAF events, almost 50% of which were identified within 30 days from the index procedure. Whether early POAF can be perpetuated and lead to recurrent AF episodes remains a topic of debate; in the present study, early POAF was not independently associated with an increased risk for late POAF, but late POAF events were numerically more frequent among patients who experienced early POAF. It is plausible that patients with minimal comorbidities, such as those included in the PARTNER 3 trial, do not frequently possess the underlying atrial remodeling profile that would provide the electric substrate for late or perpetuating AF (15). Nevertheless, in the present study, increasing LAV was a significant predictor of POAF even in this low-surgical risk population, confirming the significance of underlying structural left atrial abnormalities in the initiation and likely propagation of POAF (21). Alternatively, our findings may be partially explained by the infrequent use of continuous monitoring, thus not capturing asymptomatic AF episodes.

In the present study, we further assessed the prognostic impact of POAF according to timing of occurrence after SAVR or TAVR. Prior studies have largely focused on the prognostic implications of in-hospital POAF following TAVR or SAVR and have reported conflicting results (1-3,9,10,12-14). A recent

meta-analysis of patients with AS undergoing TAVR found that only preexisting AF, not new-onset AF, was associated with increased late mortality (11), whereas in a separate meta-analysis, new-onset AF was predictive of late mortality (5). Similarly, whether early POAF is an independent risk factor for long-term mortality following SAVR remains controversial (4,7,22). Nevertheless, as previous studies have not addressed the occurrence of AF after discharge, it remains unclear whether early POAF is a direct mediator of worse long-term survival. Interestingly, in the present analysis of patients with AS at low surgical risk, though the unadjusted rates of early (within 30 days) adverse cardiovascular outcomes were higher among patients with early POAF, development of early POAF did not confer an increased risk for mortality, stroke, or rehospitalization at 2 years. In contrast, late POAF was independently associated with the 2-year risk for death, stroke, or rehospitalization, irrespective of treatment modality. Whether late POAF is a direct risk factor or a marker of a severe or chronic atherothrombotic process, in contrast to early POAF, which may, in isolation, be a self-limiting phenomenon, cannot be fully discerned from the present study. It is plausible that patients with recurrent or new AF after discharge were more readily identified and diagnosed because of more frequent readmissions observed in this patient population; however, the increased risk for both cardiovascular readmissions and the composite outcome was ascertained via the inclusion of late AF as a time-updated variable, thus reducing selection bias. Interestingly, the higher rate of late POAF following SAVR may partially explain the increased risk for cardiovascular rehospitalization compared with TAVR; as such, identification of patients at risk for late POAF is of particular clinical relevance, especially following SAVR. Collectively, the impact of early POAF on 30-day adverse outcomes as well as the increased adjusted risk for adverse cardiovascular outcomes associated with late AF imply that vigilant cardiac rhythm monitoring and frequent clinical evaluation is crucial for several months following the index procedure. Furthermore, as complex structural interventions are more frequently tested in low-surgical risk populations, recognition and appropriate management of readily identifiable factors such as POAF, which may adversely affect an overall favorable clinical outlook, are ever more crucial and should be at the forefront of pre- and postprocedural strategy.

Last, we examined the impact of POAF following TAVR or SAVR on early or late stroke. Excluding early

TABLE 5 Unadjusted Clinical Outcomes in Patients With Versus Without Early Postoperative Atrial Fibrillation or Flutter

	30 Days			2 Years		
	Early POAF (n = 152)	No Early POAF (n = 629)	P Value	Early POAF (n = 152)	No Early POAF (n = 629)	P Value
Death, stroke, or rehospitalization	10.5 (18, 16)	5.4 (36, 34)	0.02	16.6 (30, 25)	12.0 (89, 75)	0.10
Death	1.3 (2, 2)	0.8 (5, 5)	0.54	2.7 (4, 4)	2.6 (16, 16)	0.94
All stroke	3.9 (6, 6)	0.6 (4, 4)	0.001	4.6 (7, 7)	2.1 (13, 13)	0.07
Rehospitalization	6.6 (10, 10)	4.2 (27, 26)	0.20	12.1 (19, 18)	8.7 (60, 54)	0.19
Cardiovascular death	1.3 (2, 2)	0.6 (4, 4)	0.39	2.7 (4, 4)	1.8 (11, 11)	0.47
All bleeding	29.0 (54, 44)	16.2 (114, 102)	0.0003	33.7 (63, 51)	21.0 (154, 132)	0.0007
Life-threatening bleeding	9.2 (17, 14)	5.6 (39, 35)	0.10	9.9 (18, 15)	6.9 (48, 43)	0.20
Life-threatening or major bleeding	14.5 (25, 22)	6.4 (41, 40)	0.0009	14.5 (25, 22)	8.3 (55, 52)	0.02

Rates are Kaplan-Meier estimates, % (n events, n subjects with event).
POAF = postoperative atrial fibrillation or flutter.

strokes, which are largely related to procedure-related complications, prior studies have reported conflicting results on the association between early POAF and late stroke (1,9). Interestingly, in SOURCE XT (SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry), 90.6% of surviving patients with early POAF experienced recurrent AF at 30-day follow-up and 100% at 1-year and 2-year follow-up visits; further, early POAF was found to be predictive of late stroke at 2 years (13); whether the increased risk for late stroke in these high-surgical risk AS patients could be explained by early POAF, recurrent late AF, or undetected preexisting AF was not defined. In the present study, we observed a trend toward a higher unadjusted rate of stroke at 2 years among patients with early POAF; however, this increased risk was no longer present following adjustment, including adjustment for anticoagulant therapy. In contrast, late POAF was independently associated with higher unadjusted and adjusted risk for stroke, though adjusted analyses were limited by

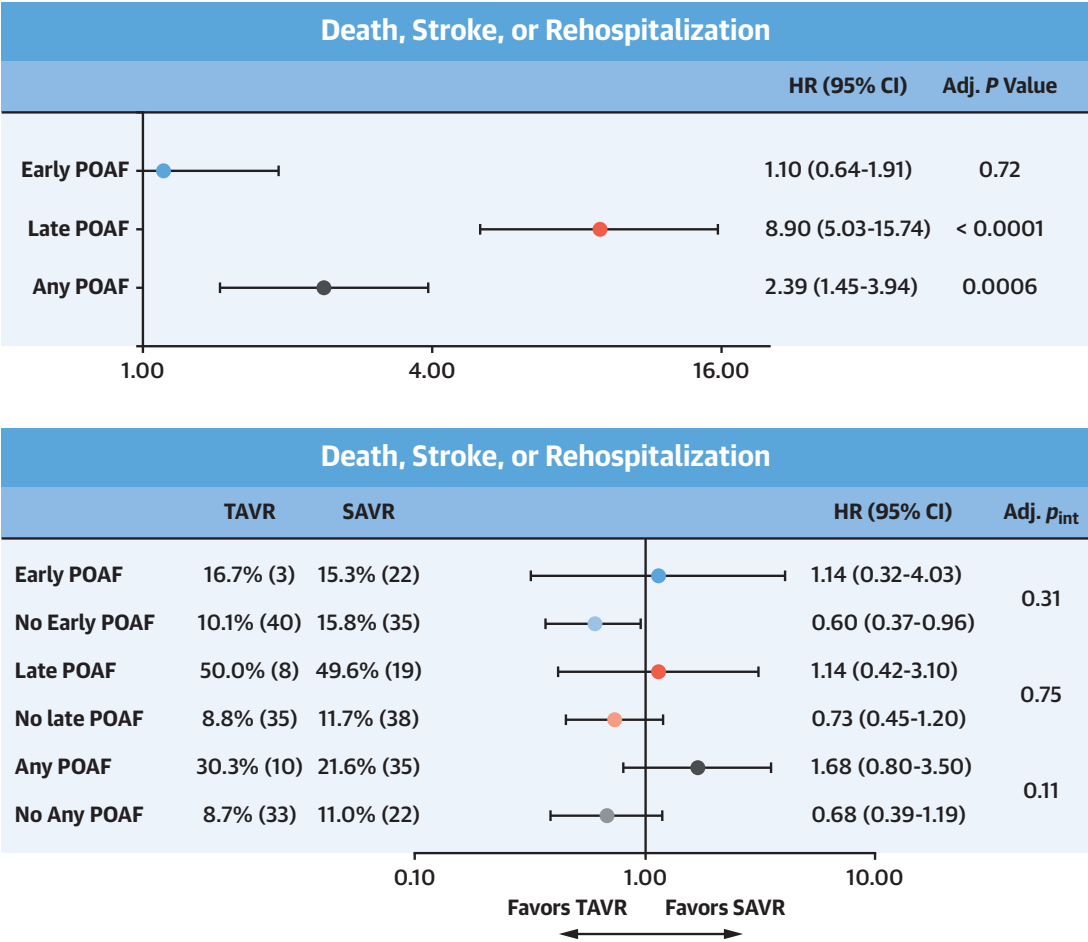
the small overall number of strokes observed in the PARTNER 3 trial. Notably, <50% of patients with early POAF were discharged on anticoagulant therapy; similarly, fewer than half of patients with late POAF were on anticoagulant agents at 1 year. The underuse of anticoagulant therapy for early POAF likely reflects the common view of early POAF as a bystander, self-limited phenomenon; in contrast, the limited use of anticoagulant therapy in patients with late POAF is possibly multifactorial, including balancing of bleeding versus embolic risk and consideration of the overall low CHA₂DS₂-VASc score in the study population. Nevertheless, in the present analysis, all patients with late POAF who had strokes were treated with anticoagulant therapy prior to the stroke events, though these findings should be interpreted cautiously, as potential confounding factors, such as medication nonadherence or subtherapeutic international normalized ratios in patients managed with warfarin were not consistently captured. Collectively, although hypothesis generating only given the low

TABLE 6 2-Year Adjusted Risk of Adverse Clinical Outcomes in Patients With Versus Without POAF According to Timing of Occurrence

	Any POAF		Early POAF		Late POAF	
	Adjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value
Death, stroke, or rehospitalization	2.39 (1.45-3.94)	0.0006	1.10 (0.64-1.91)	0.72	8.90 (5.03-15.74)	<0.0001
Death	1.83 (0.6-5.64)	0.29	1.03 (0.31-3.44)	0.96	4.49 (1.20-16.83)	0.03
All stroke	2.52 (0.77-8.31)	0.13	1.56 (0.48-5.06)	0.46	11.87 (3.05-46.15)	0.0004
Rehospitalization	2.82 (1.59-5.0)	0.0004	1.21 (0.64-2.28)	0.56	11.08 (5.81-21.15)	<0.0001
All bleeding	1.03 (0.56-1.92)	0.92	1.10 (0.77-1.58)	0.61	1.91 (0.67-5.42)	0.23
Life-threatening bleeding	0.68 (0.18-2.59)	0.57	0.86 (0.46-1.59)	0.62	3.90 (0.81-18.85)	0.09
Life-threatening or major bleeding	0.6 (0.23-1.51)	0.28	1.19 (0.68-2.08)	0.54	1.69 (0.39-7.33)	0.48

The models are adjusted for age, male sex, diabetes, hypertension, congestive heart failure, anemia, history of transient ischemic attack or stroke, body mass index, left ventricular ejection fraction, and treatment modality. The model for late POAF also includes early POAF as a covariate.
CI = confidence interval; HR = hazard ratio; POAF = postoperative atrial fibrillation or flutter.

CENTRAL ILLUSTRATION Adjusted Risk for the Composite Outcome of All-Cause Death, Stroke, or Rehospitalization According to the Presence of Early, Late, and All Postoperative Atrial Fibrillation or Flutter in Patients Undergoing Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement



Shahim, B. et al. J Am Coll Cardiol Interv. 2021;14(14):1565-74.

(Top) Adjusted 2-y risk for the composite outcome of all-cause death, stroke, or rehospitalization according to the presence of early, late, and all postoperative atrial fibrillation or flutter (POAF). POAF includes atrial fibrillation or flutter (AF) episodes occurring from the index procedure up to 1 y. Early POAF includes AF events occurring during the index hospitalization. Late POAF includes all AF episodes occurring from discharge up to 1 y following the index procedure. Any POAF includes early and late POAF. Late or any POAF were entered in the Cox model as time-updated covariates. Early POAF was included as a covariate in the model for late POAF. Late POAF and any POAF, but not early POAF, were independently associated with the composite endpoint of death, stroke, or rehospitalization. The hazard ratios were plotted on a logarithmic axis. **(Bottom)** Adjusted 2-y risk for the composite outcome of all-cause death, stroke or rehospitalization and presence of early, late, and any POAF according to treatment modality. There was no interaction between treatment modality and the varying impact of POAF (any, early, and late) on the 2-y risk for the composite outcome of all-cause death, stroke or rehospitalization. The hazard ratios were plotted on a logarithmic axis. Adj. = Adjusted ; POAF = postoperative atrial fibrillation or flutter; SAVR = surgical aortic valve replacement.

nominal incidence of cerebrovascular events, our results strongly support the need for rigorous surveillance and guideline-directed management, including well-monitored anticoagulant therapy, of late POAF (23). Last, our findings highlight the importance of monitoring and adjudication of cardiac arrhythmias beyond the initial index hospitalization period in the setting of clinical trials and registries, as a means of better defining risk factors and optimal cardiac therapies for early and late POAF.

STUDY LIMITATIONS. The present study was not prespecified in the PARTNER 3 trial protocol, and the results should thus only be considered hypothesis generating. AF during follow-up was recorded only if clinically manifest or documented by electrocardiography, and as such, asymptomatic or transient AF episodes may not have been captured. We cannot exclude some overlap between POAF and preexisting AF, because of the limited sensitivity of methods used in current clinical practice to assess for presence of AF prior to TAVR or SAVR; however, all patients with documented clinical histories of AF were excluded from the present analysis. In addition, the PARTNER trial enrolled only patients with severe AS at low surgical risk, and our results may not be applicable to patients with higher baseline operative risk. Overall rates of individual endpoints, including death, stroke, and bleeding were low, and larger dedicated studies are needed to confirm results reported in this analysis. Results from the present study confirm prior reports of higher POAF rates following SAVR compared with transfemoral TAVR (24); however, all patients in the PARTNER 3 trial underwent TAVR using transfemoral access, and as such our findings cannot be generalized to TAVR using transaortic or transapical access. Finally, the present study was not designed to determine the safety or the optimal pharmacologic approach to POAF; medication doses, international normalized ratios, and medication adherence were not captured. As such, we cannot exclude medication nonadherence and subtherapeutic anticoagulation as potential confounders in the present analyses.

CONCLUSIONS

In the randomized PARTNER 3 trial comparing TAVR and SAVR in patients with severe AS at low surgical risk, early POAF occurred more frequently after SAVR and was not an independent predictor of late POAF. Late POAF, but not early POAF, was independently associated with increased risk for the composite endpoint of death, stroke, or rehospitalization, irrespective of treatment modality.

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PERSPECTIVES

WHAT IS KNOWN? There is an ongoing controversy regarding the incidence, recurrence rate, and prognostic impact of early POAF in patients with AS at low surgical risk undergoing TAVR or SAVR; furthermore, whether late POAF occurring after discharge is associated with early POAF and affects long-term outcomes is unknown.

WHAT IS NEW? In the PARTNER 3 trial of patients with severe AS at low surgical risk, early POAF was more common than late POAF and more frequently observed after SAVR compared with TAVR. Late, but not early, POAF was independently associated with a higher risk for the composite endpoint of death, stroke, or rehospitalization at 2 years, irrespective of treatment modality.

WHAT IS NEXT? Rigorous surveillance for POAF should extend beyond the initial hospitalization. Further studies are needed to examine the predictors and optimal management of late or recurrent POAF following TAVR or SAVR.

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KEY WORDS atrial fibrillation, mortality, stroke, surgical aortic valve replacement, transcatheter aortic valve replacement

APPENDIX For a supplemental figure and tables, please see the online version of this paper.