

Atrial Fibrillation and Outcomes After Transcatheter or Surgical Aortic Valve Replacement (from the PARTNER 3 Trial)



Bahira Shahim, MD, PhD^a, S. Chris Malaisrie, MD^b, Isaac George, MD^c, Vinod H. Thourani, MD^d, Angelo B. Biviano, MD^c, Mark J. Russo, MD, MS^e, David L. Brown, MD^f, Vasilis Babaliaros, MD^g, Robert A. Guyton, MD^g, Susheel K. Kodali, MD^c, Tamim M. Nazif, MD^c, James M. McCabe, MD^h, Mathew R. Williams, MDⁱ, Philippe Généreux, MD^j, Michael Lu, PhD^k, Xiao Yu, PhD^k, Maria C. Alu, MS^{a,c}, John G. Webb, MD^l, Michael J. Mack, MD^f, Martin B. Leon, MD^{a,c}, and Ioanna Kosmidou, MD, PhD^{a,c,*}

The prognostic impact of preexisting atrial fibrillation or flutter (AF) in low-risk patients with severe aortic stenosis treated with transcatheter (TAVR) or surgical aortic valve replacement (SAVR) remains unknown. In this sub-analysis of the PARTNER 3 trial of patients with severe aortic stenosis at low surgical risk randomized 1:1 to TAVR versus SAVR, clinical outcomes were analyzed at 2 years according to AF status. Among 948 patients included in the analysis (452 [47.7%] in the SAVR vs 496 [52.3%] in the TAVR arm), 168 (17.6%) patients had AF [88/452 (19.5%) and 80/496 (16.1%) treated with SAVR and TAVR, respectively]. At 2 years, patients with AF had higher unadjusted rates of the composite outcome of death, stroke or rehospitalization (21.2% vs 12.9%, $p = 0.007$) and rehospitalization alone (15.3% vs 9.4%, $p = 0.03$) but not all cause death (3.8% vs 2.6%, $p = 0.45$) or stroke (4.8% vs 2.6%, $p = 0.12$). In adjusted analyses, patients with AF had a higher risk for the composite outcome of death, stroke or rehospitalization (hazard ratio [HR] 1.80, 95% confidence interval [CI] 1.20–2.71, $p = 0.0046$) and rehospitalization alone (HR 1.8, 95% CI 0.12–2.9, $p = 0.015$), but not death or stroke. There was no interaction between treatment modality and AF on the composite outcome ($Pinter = 0.83$).

In conclusion, preexisting AF in patients with severe AS at low surgical risk was associated with increased risk of the composite outcome of death, stroke or rehospitalization at 2 years, irrespective of treatment modality. © 2021 Elsevier Inc. All rights reserved. (Am J Cardiol 2021;148:116–123)

Atrial fibrillation or flutter (AF) is the most common comorbid arrhythmia among patients with severe aortic stenosis, observed in up to 40% of patients.^{1–6} In patients with AS at high surgical risk or deemed inoperable undergoing transcatheter aortic valve replacement (TAVR) as well as those undergoing surgical aortic valve replacement (SAVR) preexisting AF has been associated with an

increased risk of mortality and rehospitalization.^{5,7,8} Nevertheless, whether AF is a prognostic factor in low-risk patients undergoing TAVR or SAVR for severe AS remains unknown. In the present analysis of the Placement of Aortic Transcatheter Valves (PARTNER) 3 trial, we sought to determine the prognostic implications of preexisting AF in patients with severe AS at low surgical risk who underwent TAVR or SAVR.

^aCardiovascular Research Foundation, New York, New York; ^bDivision of Cardiac Surgery, Northwestern University, Chicago, Illinois; ^cNew York-Presbyterian Hospital/Columbia University Irving Medical Center, New York, New York; ^dMarcus Heart Valve Center, Piedmont Heart Institute, Atlanta, Georgia; ^eDivision of Cardiac Surgery, Rutgers-Robert Wood Johnson Medical School, New Brunswick, New Jersey; ^fBaylor Scott & White Health, Plano, Texas; ^gEmory University Medical Center, Atlanta, Georgia; ^hUniversity of Washington, Seattle, Washington; ⁱNYU Langone, New York, New York; ^jGagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey; ^kEdwards Lifesciences, Irvine, California; and ^lSt. Paul's Hospital, Vancouver, British Columbia, Canada. Manuscript received January 20, 2021; revised manuscript received and accepted February 19, 2021.

Funding: The PARTNER 3 trial was funded by Edwards LifeSciences, Irvine, California.

See page 122 for disclosure information.

*Corresponding author: Tel No: 212-3057060; fax: (646) 434-4500.

E-mail address: ik2394@cumc.columbia.edu (I. Kosmidou).

Methods

The design of the PARTNER 3 trial has been reported previously.⁴ 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 surgical aortic-valve replacement in patients with severe AS and a low risk of 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 anatomical 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.⁴ Eligible patients were randomly

assigned, in a 1:1 ratio, to undergo either TAVR with the SAPIEN 3 system or surgical aortic-valve replacement 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 signed written informed consent. Major endpoints were adjudicated by an independent clinical events committee (Cardiovascular Research Foundation, New York, New York). The primary end point was a composite of death from any cause, stroke, or rehospitalization at one year after the procedure. History of AF was assessed and determined by the enrolling sites. Patients were excluded from the current analysis if they had missing information on history of AF. For the purpose of the present study, the primary endpoint was defined a priori as the composite outcome of death from any cause, stroke or rehospitalization at 2 years. Secondary endpoints included the individual endpoints of rehospitalization due to procedure/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 VARC-2 definition. Median follow-up for clinical outcomes was 757 days and 95% of patients had complete two year data available for analysis.

All analyses were performed in the as-treated population. Continuous variables are reported as mean \pm standard

deviation and were compared using the Student t test. Categorical variables are expressed as counts and percentages and were compared with the Fisher's exact test, as appropriate. Rates of clinical outcomes were estimated using the Kaplan-Meier method and compared using the log-rank test. The adjusted associations between AF and adverse clinical outcomes were determined in Cox proportional hazards models including the following predefined clinically pertinent variables: Age, male sex, diabetes, smoking, anemia, left ventricular ejection fraction, chronic obstructive pulmonary disease, body mass index, previous percutaneous coronary intervention and treatment modality. Alternate Cox proportional hazards models including, in addition to the above noted covariates, anticoagulant therapy and concomitant MAZE procedure or left atrial appendage closure were also constructed. A 2-sided $p < 0.05$ was considered statistically significant for all tests. All statistical analyses were performed with the use of SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Among 948 patients included in the present analysis, 452 (47.7%) underwent SAVR and 496 (52.3%) underwent TAVR. History of AF was present in 168 patients (17.6%)

Table 1
Baseline characteristics of patients with versus without history of atrial fibrillation or flutter

Variable	AF (n = 168)	No AF (n = 780)	p Value
Age (years)	74.0 \pm 5.8	73.3 \pm 6.0	0.14
Men	134/168 (79.8%)	522/780 (66.9%)	0.0009
Nonwhite race or ethnic group	7/168 (4.2%)	76/780 (9.7%)	0.02
Body mass index (kg/m ²)	31.4 \pm 5.7	30.3 \pm 5.3	0.02
STS score	2.0 \pm 0.6	1.9 \pm 0.7	0.11
EuroSCORE II	1.4 \pm 0.7	1.5 \pm 1.1	0.14
NYHA class III or IV	53/168 (31.5%)	210/780 (26.9%)	0.25
CHA ₂ DS ₂ -VASc score	3.7 \pm 1.3	3.5 \pm 1.3	0.13
Coronary artery disease	49/167 (29.3%)	214/779 (27.5%)	0.63
Previous myocardial infarction	14/168 (8.3%)	40/778 (5.1%)	0.14
Previous stroke or cerebrovascular accident	9/168 (5.4%)	31/779 (4.0%)	0.40
Carotid disease	19/160 (11.9%)	91/761 (12.0%)	1.00
Peripheral vascular disease	11/167 (6.6%)	56/778 (7.2%)	0.87
Chronic obstructive pulmonary disease	9/168 (5.4%)	44/779 (5.6%)	1.00
Creatinine >2 mg/dL	0/168 (0.0%)	2/780 (0.3%)	1.00
Diabetes mellitus	56/168 (33.3%)	235/779 (30.2%)	0.46
Permanent pacemaker	9/168 (5.4%)	16/780 (2.1%)	0.03
Left bundle-branch block	7/168 (4.2%)	23/779 (3.0%)	0.46
Right bundle-branch block	18/168 (10.7%)	95/779 (12.2%)	0.69
Pulmonary hypertension	12/168 (7.1%)	35/779 (4.5%)	0.17
Hyperlipidemia	134/167 (80.2%)	631/780 (80.9%)	0.83
Hypertension	146/166 (88.0%)	662/779 (85.0%)	0.40
Congestive heart failure	71/168 (42.3%)	269/779 (34.5%)	0.06
Pulmonary disease	12/168 (7.1%)	42/779 (5.4%)	0.36
PCI or CABG	32/166 (19.3%)	143/778 (18.4%)	0.83
Anemia	12/168 (7.1%)	61/780 (7.8%)	0.87
Renal disease	17/168 (10.1%)	80/780 (10.3%)	1.00
History of alcohol abuse	15/168 (8.9%)	61/780 (7.8%)	0.64
History of cancer	29/167 (17.4%)	179/777 (23.0%)	0.12
Cirrhosis	0/168 (0.0%)	0/779 (0.0%)	—
Thrombocytopenia	2/168 (1.2%)	9/779 (1.2%)	1.00
Coagulopathy	2/168 (1.2%)	2/780 (0.3%)	0.15

Values are mean \pm standard deviation or n/N (%). AF = atrial fibrillation or flutter; CABG = coronary artery bypass surgery; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

(88 [19.5%] treated with SAVR and 80 [16.1%] treated with TAVR). Compared to patients without AF, patients with AF were more frequently male and Caucasian, and were more likely to have a history of pacemaker implant and higher body-mass index (Table 1). At discharge, 81.0% of patients with AF were on anticoagulant medication compared to 22.9% of patients without AF (Supplemental Table 1). Baseline characteristics of patients with versus without AF in the TAVR and SAVR arms were overall well balanced (Supplemental Table 2). Compared to patients without AF, patients with history of AF had lower baseline left ventricular ejection fraction, a higher prevalence of mitral and tricuspid regurgitation and larger systolic annular perimeter and systolic annular area (Table 2). Procedural

characteristics are shown in Table 3 and Supplemental Table 3. Patients with AF had longer procedure and anesthesia times and more often underwent concomitant procedures compared with patients without AF. Among patients treated with SAVR, patients with AF had longer total aortic cross clamp time and more often underwent concomitant procedures, including MAZE (22/88 [25%]) and left atrial appendage ligation (31/88 (35.2%)) compared with patients without AF (Supplemental Table 4).

In the overall study population, AF was associated with increased unadjusted rates of the primary composite outcome of death, stroke or rehospitalization at 2 years as well as the individual endpoint of rehospitalization, but not death, stroke or major bleeding (Figures 1A–D, Table 4).

Table 2

Baseline echocardiographic and computed tomography characteristics of patients with versus without history of atrial fibrillation or flutter

Variable	AF (n = 168)	No AF (n = 780)	p Value
Echocardiographic			
Aortic valve area (cm ²)	0.8 ± 0.2	0.8 ± 0.2	0.61
Aortic valve mean gradient (mm Hg)	47.7 ± 11.4	49.2 ± 12.5	0.13
Left ventricular ejection fraction (%)	64.1 ± 8.5	66.3 ± 8.8	0.004
Left atrial volume (mL)	90.2 ± 31.3	68.9 ± 20.8	<0.0001
Peak pulmonary artery systolic pressure (mm Hg)	39.4 ± 11.6	35.1 ± 9.2	0.0002
Moderate or severe regurgitation			
Aortic	6/165 (3.6%)	24/763 (3.1%)	0.81
Mitral	8/163 (4.9%)	12/749 (1.6%)	0.02
Tricuspid	9/162 (5.6%)	9/739 (1.2%)	0.002
Computed tomography			
Systolic annular perimeter (mm)	80.5 ± 7.3	77.8 ± 6.9	<0.0001
Systolic annular area, (mm ²)	503.0 ± 88.9	470.4 ± 83.5	<0.0001

Values are mean ± standard deviation (n) or n/N (%). AF = atrial fibrillation or flutter.

Table 3

Procedural characteristics of patients with versus without history of atrial fibrillation or flutter

Variable	AF (n = 168)	No AF (n = 780)	p Value
Procedure time (min)	145.4 ± 96.2	126.6 ± 88.5	0.02
Anesthesia type			
General	114/168 (67.9%)	503/780 (64.5%)	0.48
Conscious sedation	52/168 (31.0%)	271/780 (34.7%)	
Anesthesia time, min	239.0 ± 115.8	216.2 ± 105.1	0.02
Concomitant procedures	52/168 (31.0%)	102/780 (13.1%)	<0.0001
Index hospitalization (hours)	99.2 ± 6.33	93.0 ± 3.31	0.17
Intensive care unit stay (hours)	46.4 ± 3.75	47.8 ± 2.22	0.90

Values are mean ± standard deviation or n/N (%). AF = atrial fibrillation or flutter.

Table 4

Unadjusted clinical outcomes in patients with versus without history of atrial fibrillation

Variable	30 Days			2 Years		
	AF (N=168)	No AF (N=780)	p Value	AF (N=168)	No AF (N=780)	p Value
Death, stroke or rehospitalization	15/168 (8.9%)	50/780 (6.4%)	0.24	35/168 (21.2%)	100/780 (12.9%)	0.007
Death	0 (0.0%)	7/780 (0.9%)	0.22	6/168 (3.8%)	20/780 (2.6%)	0.45
All stroke	5/168 (3.0%)	10/780 (1.3%)	0.11	8/168 (4.8%)	20/780 (2.6%)	0.12
Rehospitalization	11/168 (6.6%)	36/780 (4.7%)	0.30	25/168 (15.3%)	72/780 (9.4%)	0.03
Cardiovascular death	0 (0.0%)	6/780 (0.8%)	0.25	5/168 (3.1%)	15/780 (1.9%)	0.38
All bleeding	35/168 (20.9%)	145/780 (18.6%)	0.54	43/168 (25.8%)	182/780 (23.4%)	0.54
Life-threatening bleeding	11/168 (6.5%)	48/780 (6.2%)	0.85	14/168 (8.4%)	57/780 (7.3%)	0.64
Major bleeding	23/168 (13.7%)	105/780 (13.5%)	0.99	30/168 (18.0%)	124/780 (15.9%)	0.55

Data expressed as n patients with event/N patients in group (Kaplan-Meier estimated event rate %). AF = atrial fibrillation or flutter; CI = confidence interval; HR = hazard ratio.

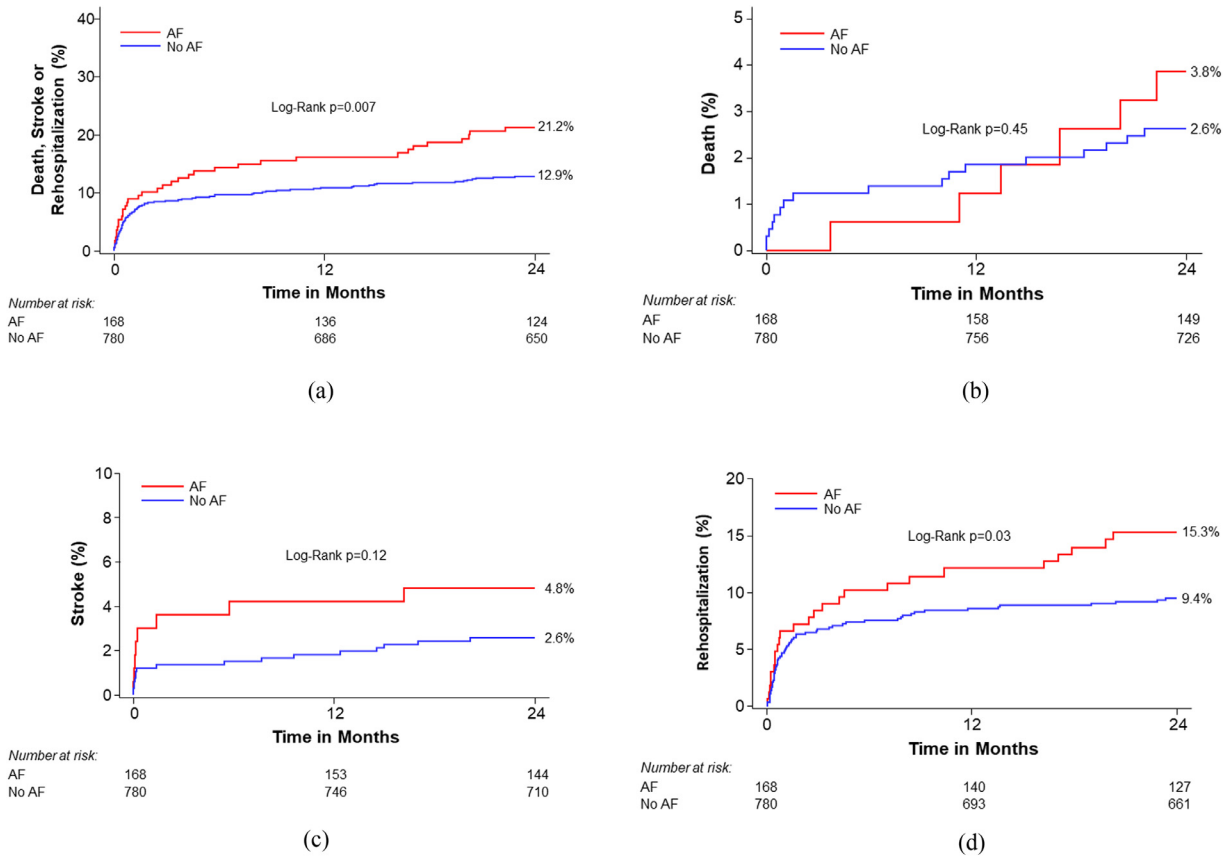


Figure 1. Kaplan-Meier time-to-first event analyses according to the presence of atrial fibrillation or flutter (A) Composite outcome of death, stroke, or rehospitalization; (B) death; (C) stroke; (D) rehospitalization. AF = atrial fibrillation or flutter.

Unadjusted clinical outcomes according to AF and treatment modality are shown in Supplemental Figure 1 (A–D). Patients with AF were more frequently rehospitalized with congestive heart failure compared with patients without AF (18/168 [10.7%] vs 15/780 [1.9%], $p = 0.002$) (Supplemental Table 5); hospitalization for heart failure accounted for 40% of readmissions among patients with AF compared with 16.9% among patients with no AF. Further, 8/168 patients with AF (4.8%) suffered a stroke at 2 years, and all were on anticoagulant therapy prior to the event.

Table 5
Adjusted clinical outcomes in patients with versus without history of atrial fibrillation or flutter at 2 years

Variable	Adjusted HR (95% CI)	p Value
Death or stroke or rehospitalization	1.80 (1.20–2.71)	0.005
Death	1.26 (0.49–3.2)	0.63
All stroke	2.11 (0.86–5.23)	0.10
Rehospitalization	1.8 (1.12–2.9)	0.02
Cardiovascular death	1.42 (0.5–4.02)	0.51
All Bleeding	0.93 (0.64–1.34)	0.69
Life-threatening bleeding	1.06 (0.56–2.02)	0.85
Major bleeding	1.01 (0.65–1.55)	0.97

Adjusted for the following covariates: age, male sex, transcatheter aortic valve replacement, diabetes, smoking, anemia, left ventricular ejection fraction, chronic obstructive pulmonary disease, body mass index, percutaneous coronary intervention. AF = atrial fibrillation or flutter; CI = confidence interval; HR = hazard ratio.

By multivariable analysis, AF was an independent predictor of the primary composite endpoint and the individual endpoint of rehospitalization, but not all-cause death, CV death, stroke or major bleeding at 2 years (Table 5). In alternate models, including adjustment for anticoagulant therapy, AF remained a significant predictor of the primary composite endpoint but not rehospitalization (Supplemental Table 6). Similarly, following adjustment for anticoagulant therapy and MAZE/LAAO, AF remained a significant predictor of the primary composite endpoint in the SAVR arm (Supplemental Table 7). There was no significant interaction between AF and treatment modality on the primary composite endpoint or the individual endpoints of all-cause death, CV death, stroke, rehospitalization or major bleeding (Figure 2A–D; Supplemental Table 8).

Changes from baseline to 1 and 2 years in 6MWT or Kansas City Cardiomyopathy Questionnaire were similar in patients with versus without AF (Supplemental Table 9).

Discussion

In the present analysis of the randomized PARTNER 3 trial of patients with severe AS at low surgical risk undergoing TAVR or SAVR: (1) history of AF was present in 17.6% of patients, (2) patients with AF had a higher risk of the primary composite endpoint of death, stroke or rehospitalization and the individual endpoint of rehospitalization at 2-years, irrespective of treatment modality, (3) AF was not

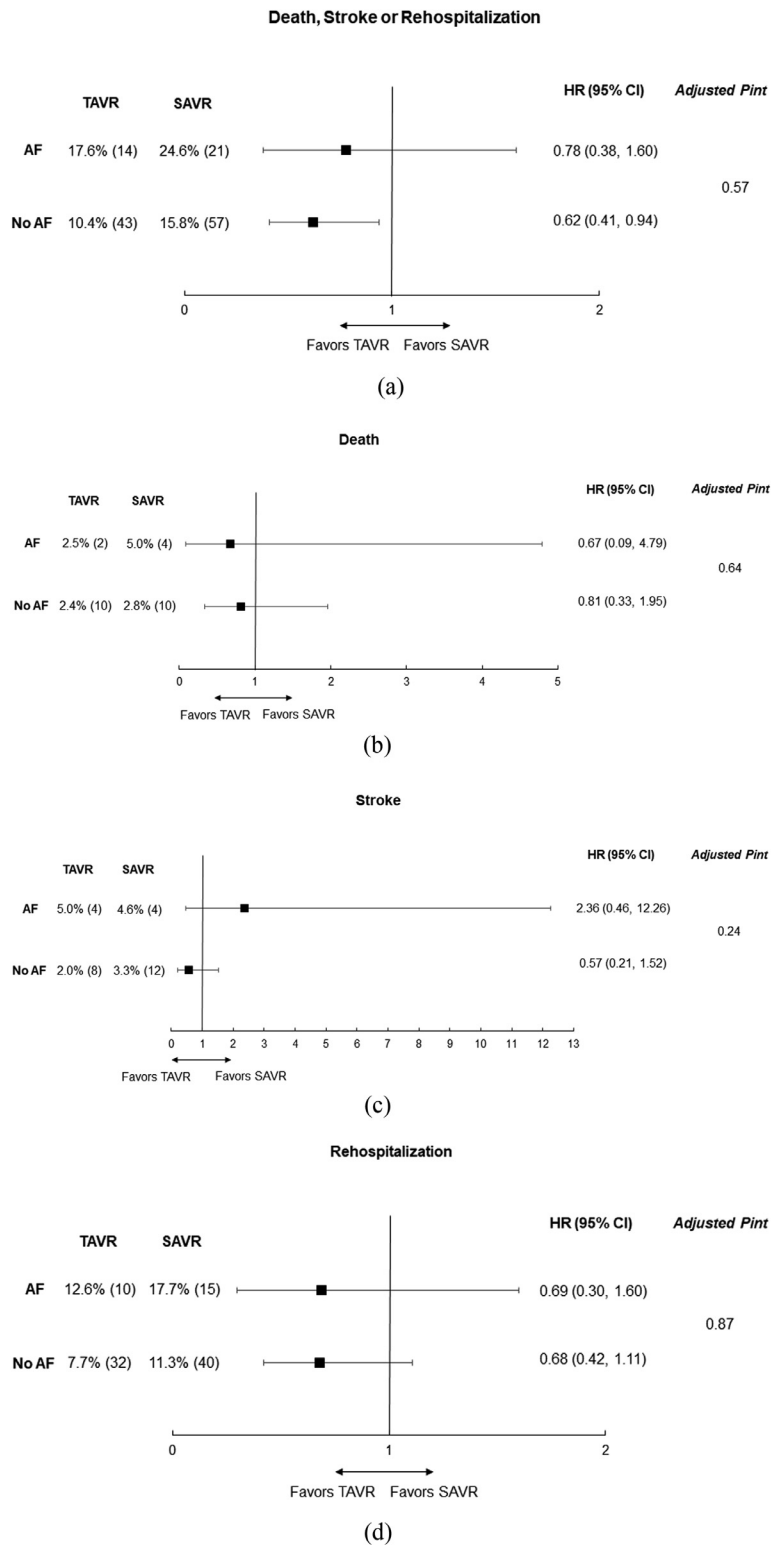


Figure 2. Adjusted two-year risk for the composite outcome of death, stroke or rehospitalization and the individual endpoints of the composite endpoint according to treatment group and history of atrial fibrillation or flutter(A) Composite outcome of death, stroke, or rehospitalization; (B) death; (C) stroke; (D) rehospitalization. In each figure the left panel shows the cumulative Kaplan-Meier estimated event rates in patients with or without history of atrial fibrillation or flutter who were randomized to transcatheter aortic valve replacement versus surgical aortic valve replacement. AF = atrial fibrillation or flutter; TAVR = transcatheter aortic valve replacement; SAVR= surgical aortic valve replacement; HR = hazard ratio; CI = confidence interval.

an independent predictor of stroke or bleeding at 2 years, and (4) there were no significant differences in change in exercise and functional capacity from baseline to 2 years in patients with versus without AF.

To the best of our knowledge, no study to date has directly assessed the prevalence and impact of preexisting AF among AS patients at low surgical risk undergoing TAVR versus SAVR. In line with findings of previous studies of higher risk cohorts^{9–11}, preexisting AF was a strong predictor of readmission following TAVR or SAVR and mainly driven by rehospitalization related to heart failure. However, mortality rate and the overall rate of AF was lower in the present low-surgical risk population compared to previously reported randomized studies and registries of higher risk cohorts^{1,7,12} in which AF conferred a 1.4 to 1.9 fold increased risk of mortality and preexisting AF was present in as many as 41% to 42% of the patients.^{13,14} Since AF can be both a possible underlying mechanism of mortality as well as a marker of underlying comorbidities and disease, it may not be surprising that in present low risk cohort, it was not a predictor of mortality.

Similarly, in the present study we found no association between AF and the risk of stroke, in accordance with prior findings based on the PARTNER trial of high risk or inoperable patients¹² and the FRANCE-2 registry of high risk patients with severe AS.¹ Although increased thromboembolic risk has often been implicated in patients with AF and AS, the pathophysiology of stroke in AS patients might be different than the one caused by non-valvular AF, when loss of mechanical function of the atrium leads to increased risk of intracardiac thrombus formation.¹⁵ The risk of stroke in AS may in part be a consequence of high atherosclerotic burden and calcific microemboli rather than stagnant flow in the left atrium.¹⁶ Accordingly, in the present study, although as many as 25% of patients with AF in the SAVR arm had concomitant MAZE and 35.2% concomitant LAA ligation, adjustment for such procedures did not affect the results. Further, all patients with AF who experienced a stroke were on anticoagulant therapy prior to the event and adjusting for anticoagulant therapy did not alter the association between AF and the risk of adverse outcomes, possibly implicating other mechanisms in the pathophysiology of stroke following TAVR or SAVR.^{17,18} There is also a possibility that anticoagulants may have protected against surgical prosthetic aortic valve thrombosis which has been associated with an increased risk of ischemic stroke^{19,20}; nevertheless, this association has not been consistently observed with transcatheter aortic valve prostheses.^{21,22} Further, even though there was no statistical difference between patients with and without AF, the raw numbers of patients with stroke in the present study were twice as high among those with AF, suggesting an aggressive atherothrombotic substrate in this patient population, which may not necessarily be responsive to anticoagulant therapy. Nevertheless, in the present study, the overall low rates of stroke, though consistent with recent reports^{23,24}, limit the ability to identify specific pathophysiologic mechanisms of cerebrovascular events.

Lastly, in the present study the risk of bleeding was similar in patients with AF compared to patients without AF, irrespective of treatment modality or anticoagulant therapy.

Other than limitations in analyzing individual endpoints, such as stroke and bleeding due to the overall rate of events, the absence of any association of AF with stroke or bleeding may alternatively be explained by careful patient selection, increasing operator experience and optimization of device platforms and techniques.²³ Further, refined postoperative and long term antiplatelet and anticoagulant management, with consideration of the balance between ischemic and bleeding risk in an overall low-risk patient population may partially explain the lack of association between AF and bleeding risk. Nevertheless, further dedicated studies are needed to address the optimal pharmacotherapy of patients with preexisting AF following SAVR or TAVR, in regard to both rhythm management as well as systemic anticoagulation, particularly in the setting of concomitant antiplatelet therapy following surgical or percutaneous aortic valve replacement.

The present study was not pre-specified in the PARTNER 3 trial protocol, and the results should thus be considered hypothesis generating. The type of AF at baseline (paroxysmal, persistent or permanent) was not captured. Furthermore, subclinical AF may have been undetected since continuous arrhythmia monitoring was not performed at baseline. Postoperative AF was not included in the present study. The PARTNER trial enrolled 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. Finally, the present study was not designed to determine the safety or the optimal pharmacologic approach to AF, and medication dosages or adjustments and INR levels were not specifically captured.

Authors' Contribution

Bahira Shahim: Conceptualization, Methodology, Writing – Original Draft, Visualization; S. Chris Malaisrie: Conceptualization, Methodology, Investigation, Resources, Writing – Review and Editing; Isaac George: Conceptualization, Methodology, Investigation, Resources, Writing – Review and Editing; Vinod H. Thourani: Conceptualization, Investigation, Resources, Writing – Review and Editing; Angelo B. Biviano: Conceptualization, Investigation, Resources, Writing – Review and Editing; Mark J. Russo: Investigation, Resources, Writing – Review and Editing; David L. Brown: Investigation, Resources, Writing – Review and Editing; Vasilis Babaliaros: Investigation, Resources, Writing – Review and Editing; Robert A. Guyton: Investigation, Resources, Writing – Review and Editing; Susheel K. Kodali: Conceptualization, Investigation, Resources, Writing – Review and Editing; Tamim M. Nazif: Investigation, Resources, Writing – Review and Editing; James M. McCabe: Investigation, Resources, Writing – Review and Editing; Mathew R. Williams: Investigation, Resources, Writing – Review and Editing; Philippe Généreux: Investigation, Resources, Writing – Review and Editing; Michael Lu: Methodology, Formal analysis, Writing – Review & Editing, Supervision; Xiao Yu: Methodology, Formal analysis, Writing – Review & Editing,

Visualization; Maria C. Alu: Methodology, Writing – Review & Editing, Supervision, Project administration; John G. Webb: Investigation, Resources, Writing – Review & Editing, Supervision; Michael J. Mack: Conceptualization, Investigation, Resources, Writing – Review & Editing, Supervision; Martin B. Leon: Conceptualization, Investigation, Resources, Writing – Review & Editing, Supervision; Ioanna Kosmidou: Conceptualization, Methodology, Investigation, Resources, Writing – Review & Editing, Supervision

Disclosures

S.C. Malaisrie is a consultant for Edwards Lifesciences, Medtronic, and Abbott. I. George is a consultant for Edwards Lifesciences. V. Thourani does research and is a consultant for Abbott Vascular, Allergan, Boston Scientific, Cryolife, Edwards Lifesciences, Gore Vascular, and Jena-valve. V Babaliarios reports institutional research funding from Abbott, Edwards Lifesciences, and Medtronic, consulting fees from Edwards Lifesciences, and equity in Transmural Systems. S.K. Kodali reports institutional research grants from Edwards Lifesciences, Medtronic, and Abbott, consulting fees from Abbott, Admedus, and Meril Lifesciences, and equity options from Biotrace Medical and Thubrikar Aortic Valve Inc. T. Nazif is a consultant for Edwards Lifesciences, Medtronic, and Boston Scientific. P. Généreux has received consultant fees from Abbott Vascular, Abiomed, Boston Scientific, Cardinal Health, Cardiovascular System Inc., Edwards Lifesciences, Medtronic, OpSens, Siemens, SoundBite Medical Solutions, Sig.Num, Saranas, Teleflex, Tryton Medical, and has equity in Pi-Cardia, Sig.Num, SoundBite Medical Solutions, Saranas, and Puzzle Medical. M. Lu and X. Yu are employees of Edwards Lifesciences. M. Alu reports institutional research support (no direct compensation) from Abbott and Edwards Lifesciences. J.G. Webb is a proctor and consultant for Edwards Lifesciences. M.J. Mack reports institutional research support (no direct physician compensation) from Edwards Lifesciences. M.B. Leon reports institutional research support from Edwards Lifesciences, Medtronic, Boston Scientific, and Abbott, and consulting/advisory board participation for Medtronic, Boston Scientific, Gore, Meril Lifescience, and Abbott. The other authors report no relevant conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2021.02.040>.

- Chopard R, Teiger E, Meneveau N, Chocron S, Gilard M, Laskar M, Eltchaninoff H, Iung B, Leprince P, Chevreul K, Prat A, Lievre M, Leguerrier A, Donzeau-Gouge P, Fajadet J, Mouillet G, Schiele F, Investigators F-. Baseline characteristics and prognostic implications of pre-existing and new-onset atrial fibrillation after transcatheter aortic valve implantation: results from the FRANCE-2 registry. *JACC Cardiovasc Interv* 2015;8:1346–1355.
- Gilard M, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetché D, Carrie D, Albat B, Cribrier A, Rioufol

- G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M, Investigators F. Registry of transcatheter aortic-valve implantation in high-risk patients. *N Engl J Med* 2012; 366:1705–1715.
- Levy F, Garayalde E, Quere JP, Ianetta-Peltier M, Peltier M, Tribouilloy C. Prognostic value of preoperative atrial fibrillation in patients with aortic stenosis and low ejection fraction having aortic valve replacement. *Am J Cardiol* 2006;98:809–811.
- Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliarios V, Goldman S, Szeto WY, Généreux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR, Investigators P. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. *N Engl J Med* 2019;380:1695–1705.
- Ngaage DL, Schaff HV, Barnes SA, Sundt TM 3rd, Mullany CJ, Dearani JA, Daly RC, Orszulak TA. Prognostic implications of preoperative atrial fibrillation in patients undergoing aortic valve replacement: is there an argument for concomitant arrhythmia surgery? *Ann Thorac Surg* 2006;82:1392–1399.
- Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarocheliere R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. *J Am Coll Cardiol* 2010;55:1080–1090.
- Rodes-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, Feindel CM, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson M, Thompson CR, Wood D, Toggweiler S, Gurchit R, Lichtenstein SV, Doyle D, DeLarocheliere R, Teoh K, Chu V, Baine K, Lachapelle K, Cheema A, Latter D, Dumesnil JG, Pibarot P, Horlick E. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. *J Am Coll Cardiol* 2012;60:1864–1875.
- Schulenberg R, Antonitsis P, Stroebel A, Westaby S. Chronic atrial fibrillation is associated with reduced survival after aortic and double valve replacement. *Ann Thorac Surg* 2010;89:738–744.
- Czarnecki A, Qiu F, Henning KA, Fang J, Jennett M, Austin PC, Ko DT, Radhakrishnan S, Wijeyesundera HC. Comparison of 1-year pre- and post-transcatheter aortic valve replacement hospitalization rates: a population-based cohort study. *Can J Cardiol* 2020;36:1616–1623.
- Khoury H, Ragalie W, Sanaiha Y, Boutros H, Rudasill S, Shemin RJ, Benharash P. Readmission after surgical aortic valve replacement in the United States. *Ann Thorac Surg* 2020;110:849–855.
- Sanchez CE, Hermiller JB Jr, Pinto DS, Chetcuti SJ, Arshi A, Forrest JK, Huang J, Yakubov SJ. Predictors and risk calculator of early unplanned hospital readmission following contemporary self-expanding transcatheter aortic valve replacement from the STS/ACC TVT registry. *Cardiovasc Revasc Med* 2020;21:263–270.
- Biviano AB, Nazif T, Dizon J, Garan H, Fleitman J, Hassan D, Kapadia S, Babaliarios V, Xu K, Parvataneni R, Rodes-Cabau J, Szeto WY, Fearon WF, Dvir D, Dewey T, Williams M, Mack MJ, Webb JG, Miller DC, Smith CR, Leon MB, Kodali S. Atrial fibrillation is associated with increased mortality in patients undergoing transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valve (PARTNER) trial. *Circ Cardiovasc Interv* 2016;9:e002766.
- Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
- Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliarios V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock

- SJ, Investigators PT . Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.
15. Potpara TS, Lip GY, Larsen TB, Madrid A, Dobreanu D, Jedrzejczyk-Patej E, Dagues N, Conducted by the Scientific Initiatives Committee EHRA. Stroke prevention strategies in patients with atrial fibrillation and heart valve abnormalities: perceptions of 'valvular' atrial fibrillation: results of the European Heart Rhythm Association survey. *Europace* 2016;18:1593–1598.
 16. Burup Kristensen C, Jensen JS, Sogaard P, Carstensen HG, Mogelvang R. Atrial fibrillation in aortic stenosis—echocardiographic assessment and prognostic importance. *Cardiovasc Ultrasound* 2012;10:38.
 17. Dangas GD, Tijssen JGP, Wohrle J, Sondergaard L, Gilard M, Mollmann H, Makkar RR, Herrmann HC, Giustino G, Baldus S, De Backer O, Guimaraes AHC, Gullestad L, Kini A, von Lewinski D, Mack M, Moreno R, Schafer U, Seeger J, Tchetchet D, Thomitzek K, Valgimigli M, Vranckx P, Welsh RC, Wildgoose P, Volkl AA, Zazula A, van Amsterdam RGM, Mehran R, Windecker S, Investigators G . A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. *N Engl J Med* 2020;382:120–129.
 18. Kosmidou I, Liu Y, Alu MC, Liu M, Madhavan M, Chakravarty T, Makkar R, Thourani VH, Biviano A, Kodali S, Leon MB. Antithrombotic therapy and cardiovascular outcomes after transcatheter aortic valve replacement in patients with atrial fibrillation. *JACC Cardiovasc Interv* 2019;12:1580–1589.
 19. Jander N, Sommer H, Pingpoh C, Kienzle RP, Martin G, Zeh W, Pache G, Siepe M, Beyersdorf F, Schumacher M, Neumann FJ, Minners J. The porcine valve type predicts obstructive thrombosis beyond the first three postoperative months in bioprostheses in the aortic position. *Int J Cardiol* 2015;199:90–95.
 20. Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Bogers AJ, Habbema JD. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation* 2001;103:1535–1541.
 21. Makkar RR, Fontana G, Jilaihawi H, Chakravarty T, Kofoed KF, De Backer O, Asch FM, Ruiz CE, Olsen NT, Trento A, Friedman J, Berman D, Cheng W, Kashif M, Jelnin V, Kliger CA, Guo H, Pichard AD, Weissman NJ, Kapadia S, Manasse E, Bhatt DL, Leon MB, Sondergaard L. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015;373:2015–2024.
 22. Vollema EM, Kong WKF, Katsanos S, Kamperidis V, van Rosendaal PJ, van der Kley F, de Weger A, Ajmone Marsan N, Delgado V, Bax JJ. Transcatheter aortic valve thrombosis: the relation between hypo-attenuated leaflet thickening, abnormal valve haemodynamics, and stroke. *Eur Heart J* 2017;38:1207–1217.
 23. Athappan G, Gajulapalli RD, Sengodan P, Bhardwaj A, Ellis SG, Svensson L, Tuzcu EM, Kapadia SR. Influence of transcatheter aortic valve replacement strategy and valve design on stroke after transcatheter aortic valve replacement: a meta-analysis and systematic review of literature. *J Am Coll Cardiol* 2014;63:2101–2110.
 24. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, Sondergaard L, Juni P, Windecker S. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. *Eur Heart J* 2016;37:3503–3512.