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New-Onset Atrial Fibrillation After Aortic Valve Replacement

Comparison of Transfemoral, Transapical, Transaortic, and Surgical Approaches

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Objectives This study sought to determine the incidence of new-onset atrial fibrillation (AF) associated with different methods of isolated aortic valve replacement (AVR)—transfemoral (TF), transapical (TA), and transaortic (TAo) catheter-based valve replacement and conventional surgical approaches.

Background The relative incidences of AF associated with the various access routes for AVR have not been well characterized.

Methods In this single-center, retrospective cohort study, we evaluated a total of 231 consecutive patients who underwent AVR for degenerative aortic stenosis (AS) between March 2010 and September 2012. Patients with a history of paroxysmal, persistent, or chronic AF, with bicuspid aortic valves, and patients who died within 48 h after AVR were excluded. A total of 123 patients (53% of total group) qualified for inclusion. Data on documented episodes of new-onset AF, along with all clinical, echocardiographic, procedural, and 30-day follow-up data, were collated.

Results AF occurred in 52 patients (42.3%). AF incidence varied according to the procedural method. AF occurred in 60% of patients who underwent surgical AVR (SAVR), in 53% after TA-TAVR, in 33% after TAo-TAVR cases, and 14% after TF-TAVR. The episodes occurred at a median time interval of 53 (25th to 75th percentile, 41 to 87) h after completion of the procedure. Procedures without pericardiotomy had an 82% risk reduction of AF compared with those with pericardiotomy (adjusted odds ratio: 0.18; 95% confidence interval: 0.05 to 0.59).

Conclusions AF was a common complication of AVR with a cumulative incidence of >40% in elderly patients with degenerative AS who underwent either SAVR or TAVR. AF was most common with SAVR and least common with TF-TAVR. Procedures without pericardiotomy were associated with a lower incidence of AF. (J Am Coll Cardiol 2014;63:1510–9) © 2014 by the American College of Cardiology Foundation

Transcatheter aortic valve replacement (TAVR) has become the preferred therapy for inoperable patients with severe aortic stenosis (AS) and a safe alternative to surgical aortic valve replacement (SAVR) in those considered at high surgical risk (1,2). The established routes of access initially included the transfemoral (TF-TAVR) and transapical (TA-TAVR) approaches, with TF-TAVR being a first-line method in many centers and TA-TAVR reserved for those without adequate femoral access. In those patients in whom neither of these approaches is feasible, additional access sites such as the transaortic (TAo-TAVR) or antegrade transseptal

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can be used (3). Although effective and with comparable results to TF-TAVR, the TA-TAVR is associated with well-described procedural and post-operative risks because it involves a lateral thoracotomy, as well as a left ventricular (LV) puncture and entrance into the pericardium (4).

New-onset atrial fibrillation (AF) after aortic valve replacement (AVR) has been underappreciated in current guidelines that report mortality and morbidity after cardiac valve interventions (5). However, recent evidence suggests that the incidence of AF may be higher than previously expected and may also be associated with cerebrovascular accidents (CVAs) after TAVR (6,7). In addition, a higher incidence of AF has been found in patients who underwent TA-TAVR (6). The incidence of AF according to various access routes for TAVR has not been well characterized. We sought to evaluate the incidence, onset, duration, and predictors of new-onset AF among patients treated with SAVR and TF-, TA-, and TAo-TAVR.

Methods

Patients and procedures. Between March 2010 and September 2012, a total of 231 consecutive patients underwent isolated AVR for symptomatic severe degenerative AS at the University of Miami Hospital. Of these, 82 patients underwent SAVR and 149 patients underwent TAVR with a balloon-expandable valve (Edwards SAPIEN, SAPIEN XT, Edwards Lifesciences, Irvine, California). Patients were excluded from this analysis if they had a history of either chronic or paroxysmal AF or any evidence of atrial arrhythmia in the baseline electrocardiogram (80 patients), a bicuspid aortic valve (24 patients), or had died within 48 h after the procedure (4 patients). The final study population was 123 patients. TAVR was performed in patients who were deemed inoperable or had a surgical mortality risk of ≥15% on the basis of the consensus of our structural heart disease team. TF-TAVR was the preferred access approach in patients with an appropriate iliofemoral arterial diameter. Otherwise, TA- or TAo-TAVR was performed. TA-TAVR was performed using a well-described technique through the LV apex (8). TAo-TAVR was performed through a mini-upper sternotomy and without pericardiotomy (9).

Although the data for this study were retrospectively collected, all patients followed a pre-specified clinical and imaging evaluation at baseline, during hospitalization, and at 30 days. Echocardiographic findings were analyzed on the basis of the judgment of full-time academic echocardiographers, using standard guidelines (10). Comorbidities were defined according to the Society of Thoracic Surgeons (STS) criteria, and procedural complications were defined according to the Valve Academic Research Consortium Criteria. Blood transfusion was recorded if the patients received any blood transfusion related to the procedures, including pre-, peri-, and post-procedures. CVAs were classified as transient ischemic attack (TIA) or stroke. Stroke was further categorized in accordance with the modified Rankin scale (MRS) as major if the MRS was ≥2 at 30 days, or minor if the MRS was <2 at 30 days. All CVAs were evaluated by a neurologist and confirmed through neuroimaging techniques.

Atrial fibrillation or flutter. Patients did not receive routine pre- or peri-operative antiarrhythmic agents to prevent or decrease the occurrence of new-onset AF. However, all surgical patients received prophylactic atrial pacing for at least 24 h post-operatively. All patients were on continuous electrocardiographic telemetry monitoring until hospital discharge. Whenever an electrocardiographic or cardiac rhythm abnormality was noted by either the nursing staff or the monitoring device, rhythm strips were printed and attached to the patient's chart. In addition, routine rhythm strips were printed and charted every 2 h in the cardiac critical care units, and every 4 h in the telemetry units, regardless of the rhythm. A 12-lead electrocardiogram was routinely performed pre-operatively, immediately after the procedure, and on post-operative days 1 and 2. Episodes of AF or atrial flutter and their respective treatment were collected by reviewing the electrocardiographic rhythm strips, 12-lead electrocardiographic tracings, nursing and physician notes, orders lists, and daily medication lists. Decisions on AF management, including treatments for rhythm and/or rate control, as well as anticoagulation, were at the discretion of the primary cardiologist and/or the cardiothoracic surgeon managing the patients.

30-day follow-up. A routine clinical follow-up was scheduled 30 days after the procedure. Patients who were not able to attend their in-person follow-up visit were contacted by phone, and their physician's offices were contacted to obtain the necessary clinical information, including vital status, complications, hospitalizations, emergency department visits, CVAs, and atrial arrhythmias. Date of CVAs or atrial arrhythmias were noted on the date of diagnosis. Five patients died before the 30-day follow-up. Complete follow-up data were available in 92% of patients.

Statistical analysis. Descriptive estimates of the distribution of each risk factor were compared among the 4 different approaches. Discrete variables are expressed as frequencies with their respective percentages. Continuous variables are presented as mean ± SD or median (25th, 75th percentile), depending on variable distribution. Continuous variables were compared using the Student *t* test or Wilcoxon rank-sum, as appropriate, or 1-way analysis of variance or

Abbreviations and Acronyms

AF = atrial fibrillation
AS = aortic stenosis
AVR = aortic valve replacement
CVA = cerebrovascular accident
LV = left ventricular
MRS = modified Rankin scale
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAo-TAVR = transaortic transcatheter aortic valve replacement
TA-TAVR = transapical transcatheter aortic valve replacement
TAVR = transcatheter aortic valve replacement
TF-TAVR = transfemoral transcatheter aortic valve replacement
TIA = transient ischemic attack

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Kruskal-Wallis test if more than 2 groups were compared. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Logistic multivariable regression analysis was performed to identify independent risk factors for AF. We developed 4 multivariable models to examine the association among the different approaches and AF. Candidate variables were selected if they had a p value <0.10 in univariate analysis and a p value <0.10 in the 2 groups' comparison of each model. In model 1, we compared each transcatheter approach versus conventional SAVR, and the variables entered in the model included STS score, history of chronic obstructive pulmonary disease, baseline LV hypertrophy on electrocardiogram, left atrial enlargement, blood transfusion, and post-procedural leukocytosis. In model 2, we compared procedures with pericardiotomy (SAVR and TA-TAVR) versus procedures without pericardiotomy (TF- and TAo-TAVR), and the variables entered in the model included a history of chronic obstructive pulmonary disease, the use of calcium channel blockers, left atrial enlargement, post-operative peak troponin elevation, and blood transfusion. In model 3, we compared procedures with thoracotomies (SAVR and TA- and TAo-TAVR) to purely percutaneous procedures (TF-TAVR), and the variables entered in the model included a history of chronic obstructive pulmonary disease, the use of calcium channel blockers, blood transfusion, bleeding complications, and baseline LV hypertrophy on electrocardiogram. In model 4, we compared conventional SAVR versus transcatheter procedures (TA-, TAo-, and TF-TAVR), and the variables entered in the model included a history of chronic obstructive pulmonary disease, blood transfusion, bleeding complications, and baseline LV hypertrophy on the electrocardiogram. All of the models were well based on the goodness-of-fit test. A 2-sided p value <0.05 was considered statistically significant. All analyses were conducted using the statistical package SAS, version 9.2 (SAS Institute, Cary, North Carolina).

Results

AVR was performed using conventional SAVR, TA-, TAo-, and TF-TAVR in 35, 36, 24, and 28 patients, respectively. Clinical and electrocardiographic data are shown in Table 1 for the total study population and for each subgroup according to the 4 techniques. More than 90% had New York Heart Association classes III to IV heart failure. The severity of AS and LV dysfunction were comparable among the subgroups. Twenty patients (57%) in the SAVR group underwent AVR through a right anterior minithoracotomy. Patients treated with SAVR had the lowest STS risk scores (mean ± SD) (5.17 ± 2.74), whereas patients treated with TA-TAVR had the highest STS scores (11.04 ± 3.16). None of these patients were on antiarrhythmic medications before the procedure.

Post-procedure hemoglobin levels were higher in patients who underwent procedures with thoracotomies because the majority of these patients (>90%) received blood transfusions. Post-procedural white blood cell level, a surrogate for inflammatory response, was highest in TA-TAVR and became significantly different among the groups at 24 to 48 and 48 to 96 h. Patients treated with SAVR and TA-TAVR were more likely to remain intubated for more than 24 h. A higher incidence of CVAs was observed in patients treated with TF-TAVR. Other post-procedural complications were not different among the 4 groups.

Patients with and without new-onset AF. Baseline characteristics among patients with and without new-onset AF are displayed in Table 2. Patients who developed AF were more likely to have chronic obstructive pulmonary disease, a higher use of calcium channel blockers, and electrocardiographic signs of LV hypertrophy. Left atrial enlargement tended to be more common in patients with AF. A higher proportion of patients with new-onset AF received blood transfusions and also had a higher white blood cell count after the first 24 h. Prolonged intubation was more commonly observed in patients with AF, whereas need for a permanent pacemaker secondary to atrioventricular block was less common in these patients. Patients who developed AF had a longer median length of stay (9 days; range, 8 to 12 days) compared with those without AF (6 days; range, 5 to 10 days) ($p < 0.01$).

Characteristic of new-onset AF. Post-procedural, new-onset AF occurred in 52 patients (42.27%), with 51 events occurring during hospital stay (Figs. 1 and 2). The incidence of new-onset AF varied with the different approaches (Fig. 1, Online Table A), but the characteristics of new-onset AF were not significantly different among the 4 groups (Fig. 2, Online Table B). In the immediate post-procedure period, all patients in the transcatheter group were in normal sinus rhythm, and those in the SAVR group were atrial-paced. New-onset AF occurred at a median time of 53 h (25th to 75th percentile, 41 to 87 h), with 41 episodes (78.84%) occurring between 24 and 96 h after AVR. The median times of AF onset were 56 h (25th to 75th percentile, 40 to 94 h) and 52 h (25th to 75th percentile, 40 to 70 h) in the SAVR and TAVR groups, respectively. More than half of the AF episodes lasted less than 24 h and spontaneously resolved without administration of antiarrhythmic agents or electrocardioversion. Twenty-five patients received amiodarone, including 2 patients who eventually underwent successful electrocardioversion. Conversion after administration of amiodarone occurred in the majority of patients who received the drug, but 11 patients remained in AF at the time of discharge, and 7 remained in AF at the 30-day follow-up. Fourteen patients were discharged on amiodarone.

All patients who developed new-onset AF had a CHA_2DS_2-VASc score ≥2, with a median score of 5.5 (5,6). Anticoagulation was initiated during hospitalization in 25 (48.07%) patients. Reasons noted for not administering anticoagulants were short duration of AF or increased bleeding risk. In 3 patients, anticoagulation was withheld due to access site bleeding despite an AF duration more than 48 h. Anticoagulation was initiated at 24 h or more after

Table 1 Population Characteristics

Variables	Total (N = 123)	SAVR (N = 35)	TA-TAVR (N = 36)	TAo-TAVR (N = 24)	TF-TAVR (N = 28)	p Value*
Clinical characteristics						
Age, yrs	84.91 ± 6.92	82.11 ± 8.14	88.28 ± 4.80	84.00 ± 6.47	84.86 ± 6.43	<0.01†
Male	59 (47.96)	19 (54.29)	15 (41.67)	9 (37.50)	16 (57.14)	0.37
Caucasian	113 (98.26)	33 (94.29)	30 (83.33)	24 (100.00)	26 (96.29)	0.42
Hispanic	20 (16.52)	7 (20.00)	3 (8.33)	7 (29.17)	3 (10.71)	0.16
NYHA functional class III–IV	101 (93.51)	29 (85.29)	31 (100.00)	22 (95.65)	19 (95.00)	<0.01
STS score	7.67 ± 3.45	5.17 ± 2.74	11.04 ± 3.16	6.60 ± 2.74	8.13 ± 5.26	<0.01†
Medical history						
Dyslipidemia	96 (78.05)	29 (82.86)	24 (66.67)	22 (91.67)	21 (75.00)	0.11
Coronary artery disease	84 (67.29)	19 (54.29)	33 (91.67)	14 (58.33)	18 (64.28)	<0.01
Peripheral artery disease	46 (37.40)	7 (20.00)	15 (41.67)	17 (70.83)	7 (25.00)	<0.01
Hypertension	108 (87.80)	29 (82.86)	31 (88.89)	24 (100.00)	24 (85.71)	0.23
Chronic kidney disease	46 (37.40)	9 (25.71)	14 (38.89)	13 (54.17)	10 (35.71)	0.17
Cerebrovascular disease	34 (27.64)	7 (20.00)	10 (27.78)	8 (33.33)	9 (32.14)	0.64
COPD	46 (37.40)	13 (37.14)	15 (41.67)	13 (54.17)	5 (17.86)	<0.01
Diabetes	45 (36.59)	14 (40.00)	10 (27.78)	7 (29.17)	14 (50.00)	0.25
Medication						
Beta blocker	71 (57.72)	14 (40.00)	27 (75.00)	17 (70.83)	13 (46.43)	<0.01
ACEI/ARB	48 (39.02)	14 (40.00)	13 (36.11)	9 (37.50)	12 (42.86)	0.95
Calcium channel blocker	25 (20.33)	9 (25.71)	10 (27.78)	4 (16.67)	2 (7.14)	0.17
Statins	86 (69.92)	23 (65.71)	23 (63.89)	19 (79.17)	21 (75.00)	0.53
Laboratory investigation						
Baseline Cr, mg/dl	1.19 ± 0.40	1.08 ± 0.32	1.24 ± 0.43	1.24 ± 0.36	1.23 ± 0.49	0.31†
Baseline Hb, g/dl	11.77 ± 2.14	12.78 ± 3.26	11.42 ± 1.03	11.24 ± 1.69	11.40 ± 1.38	<0.01*
First 24-h peak Cr, mg/dl	1.28 ± 0.43	1.23 ± 0.44	1.26 ± 0.43	1.30 ± 0.34	1.33 ± 0.51	0.83†
24–48 h peak WBC, $10^3/\mu l$	12.41 ± 5.05	12.10 ± 4.29	14.32 ± 3.99	12.08 ± 4.53	10.66 ± 6.71	0.03†
24–48 h nadir Hb, g/dl	10.51 ± 1.67	11.07 ± 1.47	10.86 ± 1.52	10.07 ± 1.25	9.75 ± 2.05	<0.01†
48–96 h peak WBC, $10^3/\mu l$	11.34 ± 4.73	11.73 ± 4.54	13.06 ± 4.41	10.40 ± 3.87	9.40 ± 5.37	<0.01‡
48–96 h nadir Hb, g/dl	10.16 ± 1.75	10.77 ±1.59	10.65 ± 1.45	9.72 ± 1.19	9.13 ± 2.23	<0.01†
Post-operative peak troponin (ng/ml)	3.82 ± 0.44	7.25 ± 4.93	6.02 ± 5.03	2.04 ± 1.70	1.67 ± 3.32	<0.01†
Electrocardiogram						
Baseline LVH	21 (17.07)	11 (31.43)	8 (22.86)	1 (4.17)	1 (3.57)	<0.01
Echocardiogram						
Ejection fraction, %	56.63 ± 12.71	60.71 ± 5.56	56.36 ± 13.08	56.67 ± 11.51	52.86 ± 17.07	0.15†
Mean aortic gradient, mm Hg	44.09 ± 14.76	41.93 ± 14.33	43.88 ± 11.34	45.78 ± 18.26	44.82 ± 16.15	0.83†
Aortic valve area, cm^2	0.67 ± 0.19	0.76 ± 0.23	0.63 ± 0.18	0.66 ± 0.17	0.65 ± 0.18	0.08†
Mitral regurgitation	87 (77.00)	20 (71.43)	30 (85.71)	17 (73.91)	20 (74.07)	0.44
Left atrial size						
Mild enlargement	44 (37.60)	13 (41.93)	19 (52.78)	4 (18.18)	8 (28.57)	0.02
Moderate and severe enlargement	19 (16.23)	7 (22.58)	6 (16.67)	3 (13.64)	3 (10.71)	
Diastolic function						0.14
Grade I	87 (75.00)	24 (80.00)	27 (75.00)	19 (86.36)	17 (60.71)	
Grade II–III	23 (19.83)	3 (10.00)	9 (25.00)	2 (9.09)	9 (32.14)	
Procedure						
Blood transfusion	104 (84.55)	32 (91.43)	35 (97.22)	22 (91.67)	15 (53.57)	<0.01
Complications						
Required permanent pacemaker	10 (8.13)	2 (5.71)	2 (5.56)	3 (12.50)	3 (10.71)	0.80
Stroke or TIA	5 (4.06)	0 (0.00)	1 (2.78)	0 (0.00)	4 (14.29)	0.02
Renal insufficiency	39 (31.70)	9 (25.71)	16 (44.44)	8 (33.33)	6 (21.43)	0.45
Prolonged intubation	38 (30.89)	16 (45.71)	16 (44.44)	5 (20.83)	1 (3.57)	<0.01
Bleeding	64 (52.03)	18 (51.43)	15 (46.88)	17 (70.83)	14 (50.00)	0.32

Values are n (%) or mean ± SD. *Chi-square test. †Analysis of variance test. ‡Kruskal-Wallis test.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blockers; Cr = creatinine; COPD = chronic obstructive pulmonary disease; Hb = hemoglobin; LVH = left ventricular hypertrophy; NYHA = New York Heart Association functional classification; RVSP = right ventricular systolic pressure; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; TAo-TAVR = transaortic transcatheter aortic valve replacement; TA-TAVR = transapical transcatheter aortic valve replacement; TIA = transient ischemic attack; WBC = white blood cell count.

Table 2 Population Characteristics: No Atrial Fibrillation (AF) Versus AF

Variables	No AF (N = 71)	AF (N = 52)	p Value
Clinical characteristics			
Age, yrs	84 ± 7.42	86 ± 6.05	0.10
Male	36 (50.70)	23 (44.23)	0.48
Caucasian	67 (98.53)	46 (97.87)	0.34
NYHA functional class III–IV	58 (96.67)	43 (91.49)	0.52
STS score	7.35 ± 3.94	8.13 ± 4.55	0.35
Medical history			
Coronary artery disease	51 (71.83)	33 (63.46)	0.32
Peripheral artery disease	28 (39.44)	18 (34.62)	0.59
Hypertension	63 (88.73)	45 (86.54)	0.71
Chronic kidney disease	28 (39.44)	18 (34.62)	0.59
Cerebrovascular disease	19 (26.76)	15 (28.85)	0. 80
COPD	20 (28.17)	26 (50.00)	<0.01
Diabetes	31 (43.66)	14 (26.92)	0.06
Medication			
Beta-blocker	40 (56.34)	31 (59.62)	0.71
ACEI/ARB	30 (42.25)	18 (34.62)	0.39
Calcium channel blocker	5 (7.04)	20 (38.46)	<0.01
Statins	50 (70.42)	36 (69.23)	0.89
Laboratory investigation			
Baseline Cr, mg/dl	1.21 ± 0.40	1.16 ± 0.42	0.32
Baseline Hb, g/dl	11.62 ± 1.25	11.97 ± 2.96	0.86
24–48 h peak WBC, $10^3/\mu l$	11.95 ± 5.46	13.00 ± 4.47	0.04
24–48 h nadir Hb, g/dl	10.16 ± 1.80	10.94 ± 1.37	<0.01
48–96 h peak WBC, $10^3/\mu l$	10.60 ± 4.63	12.31 ± 4.72	0.05
48–96 h nadir Hb, g/dl	9.76 ± 1.93	10.66 ± 1.35	<0.01
Post-operative peak troponin, ng/ml	3.08 ± 3.79	4.94 ± 5.11	0.07
Electrocardiogram			
Baseline LVH	8 (11.44)	13 (25.00)	0.05
Echocardiogram			
Ejection fraction, %	55.15 ± 14.24	58.69 ± 10.00	0.31
Mean aortic gradient, mm Hg	44.79 ± 16.06	43.02 ± 12.61	0.99
Aortic valve area, cm^2	0.67 ± 0.20	0.68 ± 0.19	0.66
Left atrial size			0.06
Mild enlargement	20 (29.85)	24 (48.00)	
Moderate and severe enlargement	9 (13.43)	10 (20.00)	
Diastolic function			0.65
Grade I	52 (77.61)	35 (71.43)	
Grade II–III	13 (19.40)	10 (20.40)	
Procedure			
Blood transfusion	57 (80.28)	47 (94)	0.03
Complications			
Required permanent pacemaker	7 (9.86)	3 (5.77)	0.04
Stroke or TIA	3 (4.17)	2 (3.92)	0.92
Renal insufficiency	19 (26.76)	20 (38.46)	0.36
Prolonged intubation	16 (22.54)	22 (42.31)	<0.01
Bleeding	36 (52.94)	28 (57.14)	0.65

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

onset of AF in 11 patients. At hospital discharge, 17 patients (32%) remained on anticoagulation. All anticoagulated patients received bridging therapy with intravenous unfractionated heparin.

Predictors of new-onset AF. Clinical factors associated with the occurrence of new-onset AF were history of chronic obstructive pulmonary disease, moderate to severe left atrial enlargement, and blood transfusions. However, after multivariable analysis, none of these factors were independently associated with new-onset AF (Table 3).

We identified a significant variation in the incidence of new-onset AF on the basis of the different procedural approaches (Table 3). AF occurred in 60% (21 of 35) of patients who underwent SAVR, in 53% (19 of 36) with

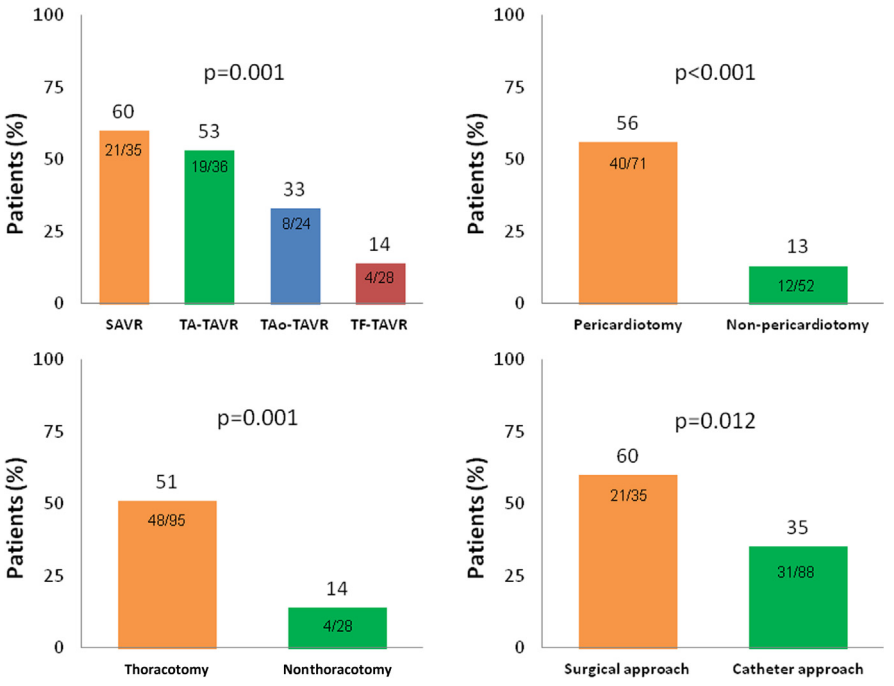

Figure 1 **Incidence of New-Onset Atrial Fibrillation in Aortic Valve Replacement**

The overall 42% incidence of new-onset AF after AVR (52 of 123 qualifying patients) is subgrouped according to technical factors, specific procedures **(upper left panel)**, with pericardiotomy versus nonpericardiotomy **(upper right panel)**, with or without thoracotomy **(lower left panel)**, and surgical versus catheter-based approach **(lower right panel)**. The incidence was highest with the conventional surgical approach, which corresponded to requirements for chest wall incision and pericardiotomy. Transapical transcatheter aortic valve replacement (TA-TAVR) also has a higher incidence of new-onset atrial fibrillation than did transaortic transcatheter aortic valve replacement (TAo-TAVR) or transfemoral transcatheter aortic valve replacement (TF-TAVR). AVR = aortic valve replacement; SAVR = surgical aortic valve replacement.

TA-TAVR, in 33% (8 of 24) with TAo-TAVR, and in 14% (4 of 28) with TF-TAVR (Fig. 1, Online Table A). By analyzing according to variations in procedural technical requirements, we observed that new-onset AF occurred in 56% of those who required pericardiotomy, 51% of those with thoracotomies and 35% of procedures using the transcatheter approach. By multivariable analysis, TF-TAVR was associated with an 82% decrease in the risk of new-onset AF compared with SAVR (adjusted odds ratio [AOR]: 0.18; 95% confidence interval [CI]: 0.04 to 0.81), and procedures without pericardiotomy were associated with 82% risk reduction (AOR: 0.18; 95% CI: 0.05 to 0.59) of new-onset AF compared with procedures with pericardiotomy (Tables 3 and 4).

Systemic embolism and cerebrovascular accidents. There were no episodes of systemic embolism or hemorrhagic stroke. Five patients developed ischemic CVA after the procedure: 1 patient in the TA-TAVR group and 4 patients in the TF-TAVR group (Online Table C). Of these, 3 patients in the TF-TAVR group did not have AF, and the CVAs occurred at 1, 2, and 5 days after the procedure, respectively. The other 2 patients developed TIAs at approximately 1 month after the procedure. Both were in AF at the time of the diagnosis and were not on anticoagulation. The patient treated with TF-TAVR was discharged 5 days after the procedure and was diagnosed with AF and TIA at the 30-day follow-up visit. The patient treated with TA-TAVR had a post-procedural course complicated by bleeding and prolonged intubation, had persistent AF, and was not on anticoagulation at the time of the TIA diagnosis (day 28).

Discussion

The present study describes the occurrence and characteristics of new-onset AF in a cohort of elderly patients with severe symptomatic AS treated with either SAVR or TAVR using TF-, TA-, or TAo-TAVR approaches. New-onset AF occurred in 42% of the studied population: 60% in the SAVR group and 35% in the TAVR groups. Within the TAVR groups, AF occurred most frequently in TA-TAVR, followed by TAo- and TF-TAVR, respectively (Fig. 1, Online Table A). The characteristics of new-onset AF were similar among each of these subgroups, but we observed significant differences in AF incidence among TAVR patient subgroups, on the basis of the approach and the need for pericardiotomy.

Although post-operative AF after SAVR has been extensively studied, there are limited data on the occurrence of new-onset AF following the different TAVR approaches. TF-TAVR is the only procedure involving percutaneous

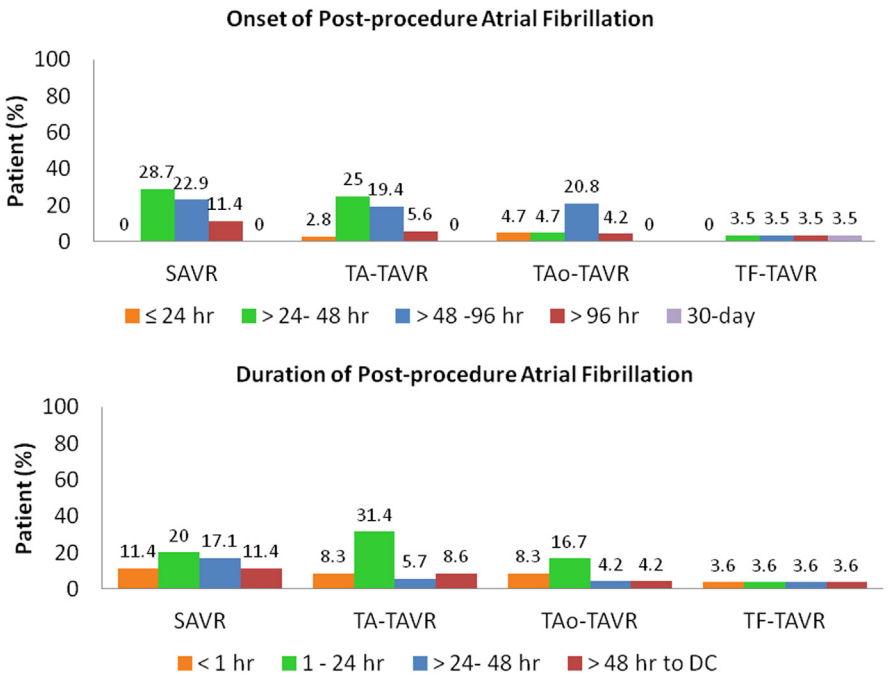

Figure 2 **Timing and Duration of Post-Procedural Atrial Fibrillation in the Different Approaches**

The distribution of times to onset of post-procedural atrial fibrillation is provided in the upper panel. The majority of events occurred between 24 and 96 h after the procedure. The most common duration of first episodes (lower panel) was between 1 and 24 h (Online Table B).

access alone, whereas TA- and TAo-TAVR involve minimal invasive surgery through left lateral and upper midline thoracotomies, respectively. This study demonstrated the differences in AF occurrence among the various TAVR approaches compared with traditional SAVR. SAVR was associated with the highest incidence of AF among the groups studied. This incidence was higher than the 24% to 49% that was reported previously when a right anterior minithoracotomy was performed (11–13). This was possibly due to the advanced age, multiple comorbidities, lack of pre-operative pharmacologic interventions, and increased surveillance with continuous telemetry monitoring in our cohort (14).

With regard to the differential incidence of AF associated with the various transcatheter approaches, the currently

Table 3 **Incidence and Predictors of Post-Procedural Atrial Fibrillation**

Variables	Incidence of AF	Adjusted Odds Ratio (95% CI)
Nonpericardiotomy vs. pericardiotomy		
Procedures with nonpericardiotomy (N = 52)	12 (23.08)	0.18 (0.05–0.59)
Nonthoracotomy vs. thoracotomy		
Procedures with nonchest wall incision (N = 28)	4 (14.29)	0.32 (0.08–1.29)
Catheter approach vs. surgical approach		
Procedures with catheter approach (N = 88)	31 (35.23)	0.64 (0.24–1.70)
SAVR vs. TA-, TAo-, TF-TAVR		
Transapical approach (N = 36)	19 (52.78)	0.53 (0.17–1.62)
Transaortic approach (N = 24)	8 (33.33)	0.40 (0.12–1.37)
Transfemoral approach (N = 28)	4 (14.29)	0.18 (0.04–0.81)
STS score > 10 (N = 33)	19 (57.58)	2.92 (0.94–9.10)
History of COPD (N = 46)	26 (56.52)	2.06 (0.87–4.89)
Baseline LVH on electrocardiogram (N = 21)	13 (61.90)	1.39 (0.54–3.59)
Moderate to severe left atrial enlargement (N = 19)	10 (52.63)	2.49 (0.98–6.33)
Blood transfusion (N = 104)	47 (45.19)	1.22 (0.23–6.32)
Post-procedural leukocytosis (N = 53)	27 (50.94)	1.66 (0.70–3.97)

Values are n (%).

AF = atrial fibrillation; CI = confidence interval; TF-TAVR = transfemoral transcatheter aortic valve replacement; other abbreviations as in Table 1.

Table 4 Population Characteristics: Pericardiotomy Versus Nonpericardiotomy

Variables	Procedure With Pericardiotomy (N = 71)	Procedure Without Pericardiotomy (N = 52)	p Value
Clinical characteristics			
Age, yrs	85.23 ± 7.30	84.46 ± 6.40	0.53
Male	34 (47.89)	25 (48.08)	0.98
Caucasian	63 (98.44)	50 (98.04)	0.36
NYHA functional class III–IV	60 (84.51)	41 (78.85)	0.85
STS score	7.88 ± 4.15	7.41 ± 4.30	0.28
Medical history			
Coronary artery disease	52 (73.24)	32 (61.54)	0.17
Peripheral artery disease	22 (30.99)	24 (46.15)	0.07
Hypertension	60 (84.51)	48 (92.31)	0.19
Chronic kidney disease	23 (32.39)	23 (44.23)	0.18
Cerebrovascular disease	17 (23.94)	17 (32.69)	0.28
COPD	28 (39.44)	18 (34.61)	<0.01
Diabetes	24 (33.80)	21 (40.38)	0.45
Medication			
Beta-blocker	41 (57.75)	30 (57.69)	0.99
ACEI/ARB	27 (38.03)	21 (40.38)	0.79
Calcium channel blocker	19 (26.76)	6 (11.54)	0.04
Statins	46 (64.79)	40 (76.92)	0.15
Laboratory investigation			
Baseline Cr, mg/dl	1.16 ± 0.39	1.23 ± 0.43	0.24
24–48 h peak WBC, $10^3/\mu l$	13.23 ± 4.26	11.32 ± 5.79	<0.01
24–48 h nadir Hb, g/dl	10.96 ± 1.49	9.89 ± 1.72	<0.01
48–96 h peak WBC, $10^3/\mu l$	12.40 ± 4.49	9.88 ± 4.69	<0.01
48–96 h nadir Hb, g/dl	10.71 ± 1.51	9.41 ± 1.80	<0.01
Post-operative peak troponin, ng/ml	6.18 ± 4.96	1.85 ± 2.68	<0.01
Electrocardiogram			
Baseline LVH	19 (27.14)	2 (3.85)	<0.01
Echocardiogram			
Ejection fraction, %	58.29 ± 10.58	54.61 ± 14.76	0.08
Mean aortic gradient, mm Hg	43.07 ± 12.58	45.25 ± 16.97	0.48
Aortic valve area, cm^2	0.69 ± 0.21	0.65 ± 0.17	0.40
Left atrial size			<0.01
Mild enlargement	32 (27.35)	12 (24.00)	
Moderate and severe enlargement	13 (18.30)	6 (11.53)	
Diastolic function			0.93
Grade I	51 (77.27)	36 (72.00)	
Grade II–III	12 (18.19)	11 (22.00)	
Procedure			
Blood transfusion	67 (97.10)	37 (71.15)	<0.01
Complications			
Required permanent pacemaker	4 (5.63)	6 (11.54)	0.39
Stroke or TIA	1 (1.41)	4 (7.69)	0.08
Renal insufficiency	25 (35.21)	14 (26.92)	0.57
Prolonged intubation	32 (49.25)	6 (11.54)	<0.01
Bleeding	33 (49.25)	31 (62.00)	0.17

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

available data are limited, and the incidence of AF varies on the basis of population, definition of AF, and monitoring method. In the high-risk cohort of the PARTNER (Placement of Aortic Transcatheter Valve) study, which used an electrocardiographic core laboratory to validate AF after TAVR and might not have included short episodes, new-onset AF occurred in only 8.6% of patients at 30 days (2). Similarly, Motloch et al. (15) used 72-h post-procedural monitoring and a definition of AF as episodes lasting more than 10 min; they found new-onset AF in 5 patients (11.6%) in the TA-TAVR group versus no episodes in the TF-TAVR group. That study, however, included patients with pre-existing AF, which was up to 32% of the TAVR group. The only prospective cohort

evaluating new-onset AF in patients who underwent TAVR due to either high or prohibitive operative risk was recently reported by Amat-Santos et al. (6), who demonstrated 32% of new-onset AF within 30 days after TAVR. That study included any AF episodes that lasted more than 30 s, and all the patients were on electrocardiographic monitoring until discharge from the hospital. By this method, new-onset AF occurred in 6 patients (15.79%) who underwent TF-TAVR and 38 patients (38%) who underwent TA-TAVR (6). The results of that study were comparable to ours with respect to the TF group (Fig. 2). However, our TA-TAVR cohort appeared to have a much higher incidence (up to 53%). All patients in the TA-TAVR group were considered inoperable with a high STS score compared with the study by Amat-Santos et al. The higher comorbidities (STS score, 11.0 ± 3.4 vs. 7.4 ± 4.8) and the older population group (age, 88 ± 5 years vs. 79 ± 8 years) might contribute to the higher incidence of AF in our TA-TAVR group. The incidence of new-onset AF in TAo-TAVR was not previously reported. The study by Nombela-Franco et al. (7) was the only study that included patients who underwent TAo-TAVR, reporting 12% of new-onset AF and its relation to CVA at ≤30 days. However, more than two-thirds of enrolled patients underwent TF-TAVR, and TAo-TAVR accounted for only 0.4% of populations. Together, these studies suggested that the actual incidence of AF in TAVR was higher than previously appreciated.

The development of post-operative AF is likely multifactorial. Potential precipitating factors can be classified as either acute factors caused by the intervention or chronic as related to structural heart disease and aging of the heart. In terms of acute factors, the SAVR and different approaches of TAVR contribute to different known factors associated with new-onset AF after the procedures. Inflammatory processes during cardiopulmonary bypass used in SAVR, atrial inflammation, and transient sterile pericarditis occurred in procedures with pericardiotomy, and high sympathetic tone from thoracotomy was reported as the contributing mechanism of new-onset AF (14,16–19). In our study, procedures without pericardiotomy were associated with an 82% lower risk of new-onset AF in multivariate analysis (Table 3). Blood transfusion was also associated with post-operative AF, with studies reporting an 18% increase in the odds for developing AF per unit of red blood cells transfused (20–23). Although not statistically significant with multivariate analysis, patients who received blood transfusions trended toward having a higher rate of new-onset AF after the procedure.

Pericardiotomy appears to be the most important acute factor associated with new-onset AF in our study. This finding might explain the higher incidence of new-onset AF in TA-TAVR compared with TF-TAVR in previous studies (2,6,15). When accompanied with the report of less complicated and faster post-operative recovery in TAo-TAVR, compared with TA-AVR, it might support the consideration of using TAo-TAVR as the second-line approach when TF-TAVR is not feasible (9,24).

In terms of chronic factors, advancing age was found to be the strongest predictor of post-operative AF (25). Association with other risk factors, including left atrial enlargement, body mass index, renal insufficiency, hypertension, diastolic dysfunction, and history of chronic obstructive pulmonary disease showed a large degree of variability between different studies, which was most likely due to the different populations (14). The significantly higher use of calcium channel blockers in those who developed AF might reflect the higher degree of severity of hypertension, rather than the contributing risk from medication itself. In our study, no clinical risk factors were found to be significantly associated with post-operative AF.

The temporal distribution analysis showed that the majority of post-operative AF events in our patients (78.84%) occurred in the interval between 24 and 96 h after the procedure, with the median time of onset at 53 h (range: 41 to 87 h). More than 60% of these episodes lasted less than 24 h. The timing of onset and duration of new-onset AF were not significantly different among the various subgroups. These findings were in accord with post-operative AF reported in patients who underwent conventional SAVR. It was, however, different from the previous reports in patients who underwent TAVR that showed a more variable time course (6,15). All of our patients were in sinus rhythm on the 12-lead electrocardiogram at the immediate post-operative period, and there were no AF episodes noted during the procedure in our patients. We hypothesized that procedural techniques might play a role in AF occurring during the procedure.

The most concerning aspect of new-onset AF was its relationship with CVA, particularly in the subacute period (7), and the resulting need for anticoagulation. In our study, all patients had a high $CHADS_2$ and CHA_2DS_2-VASc score, with a minimum of $CHADS_2$ score of 1 (Online Table B). Five patients in our study developed stroke or TIA after TAVR. All patients with stroke or TIA without new-onset AF developed the stroke within 1 week, whereas those with a history of new-onset AF experienced the event within the first month of the procedure. Neither of these 2 patients was anticoagulated at the time of the stroke or TIA diagnosis. The higher risk of new-onset AF in the TA-TAVR group might explain the similar risk of stroke in the TF- and TA-TAVR approaches at 30 days (7). Although 1 potential mechanism for stroke risk in the TF-TAVR cohort might be manipulation of the delivery system through the diseased aorta, a contributing factor in TA-TAVR might be new-onset AF. These findings highlighted the importance of prevention, prompt diagnosis, and treatment in the patients who develop new-onset AF. Nonetheless, using anticoagulation frequently poses a significant clinical problem due to high risk of bleeding events, either from the access site or from the combined use of dual antiplatelet therapy. Further evaluation of preventive strategies in those patients at higher risk of bleeding post-TAVR is warranted.

Study limitations. This study was limited by its small population size, single-center source, and retrospective nonrandomized design. The lack of pre-procedural electrocardiographic monitoring and the nature of being a referral center might have led to underestimation of the pre-existing paroxysmal atrial arrhythmia. Interobserver variability of echocardiographic interpretation remained an issue, especially subjective evaluation for severity of pathology. Obtaining the multidimensional measurement and volume of the left atrium might provide a better accuracy and reproducibility of its relation with new-onset AF. In addition, the incidence of new-onset AF following AVR was subject to underestimation, on the basis of the limitations imposed by routine 2- or 4-h post-procedure printouts of monitoring tracings and lack of extended monitoring after discharge. Although a valid concern, this limitation likely had a small effect on the basis the time and duration of the majority of AF events in this study (Fig. 2). All treatment data in our study were observational, so it should only be used for hypothesis-generating purposes, with limited value due to the heterogeneity of therapeutic strategies. For the diagnosis of stroke or TIA, no routine imaging studies were performed, and the diagnostic investigations were performed on the basis of clinical findings.

Conclusions

Despite its limitations, this was the first study to evaluate the incidence of new-onset atrial fibrillation among elderly patients with degenerative AS who underwent SAVR compared with different TAVR approaches. New-onset AF was found in more than 40% of patients, with the highest incidence in the surgical group, followed by TA-, TAo-, and TF-TAVR approaches, respectively. Pericardiotomy appeared to be the most important technical factor associated with new-onset AF. Randomized controlled trials studying the impact of access site on the incidence of AF in TAVR are warranted.

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Key words: atrial fibrillation ▪ transcatheter aortic valve replacement.

APPENDIX

For supplemental tables, please see the online version of this article.