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Apixaban in Patients With Atrial Fibrillation After Transfemoral Aortic Valve Replacement

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ABSTRACT

OBJECTIVES The aims of this study were to assess the impact of atrial fibrillation (AF) on outcome in transfemoral aortic valve replacement (TAVR) and to evaluate the safety and efficacy of apixaban compared with a vitamin K antagonist (VKA) in patients with AF after TAVR.

BACKGROUND Non-VKA oral anticoagulant agents have not been systematically used in patients with AF after TAVR.

METHODS Of the 617 patients enrolled, 55.9% (n = 345) were in sinus rhythm and 44.1% (n = 272) in AF. Clinical follow-up was performed after 30 days and 12 months.

RESULTS The early safety endpoint at 30 days was significantly more frequent in patients with AF compared with those in sinus rhythm (23.2% vs. 11.0%; $p < 0.01$). During 12-month follow-up, the secondary endpoint of all-cause mortality and stroke was significantly higher in patients with AF (20.6% vs. 9.7%; $p = 0.02$), driven by a significantly higher rate of all-cause mortality (19.1% vs. 7.8%; $p = 0.01$). Among patients with AF, 141 (51.8%) were treated with apixaban and 131 (48.2%) with a VKA. There was a significantly lower rate of the early safety endpoint in patients with AF treated with apixaban compared with patients treated with a VKA (13.5% vs. 30.5%; $p < 0.01$), with a numerically lower stroke rate (2.1% vs. 5.3%; $p = 0.17$) at 30 days and 12 months (1.2% vs. 2.0%; $p = 0.73$) of follow-up.

CONCLUSIONS In patients undergoing TAVR, AF was associated with a significantly higher rate of all-cause mortality throughout 12 months follow-up. The early safety endpoint in patients with AF on apixaban was significantly less frequent compared with patients receiving a VKA. (J Am Coll Cardiol Intv 2017;10:66–74) © 2017 by the American College of Cardiology Foundation.

Transfemoral aortic valve implantation (TAVR) has been shown to be superior to surgical aortic valve replacement in patients at high and intermediate surgical risk (1,2). The presence of atrial fibrillation (AF) in this older patient population is high and increases the long-term risk for thrombotic events. Although risk for stroke is highest during the valve implantation procedure, there is a continuously increasing rate of stroke within 30 days and 12 months. In the randomized PARTNER 2 (Placement of Aortic Transcatheter Valves) trial, the frequency of stroke in patients undergoing TAVR was 5.5% after 30 days and 8.0% after 12 months, with 404 patients in AF (2).

In patients with nonvalvular AF, non-vitamin K antagonist (VKA) oral anticoagulant agents (NOACs) have been shown to be superior to warfarin (3-6). Apixaban was superior to warfarin in preventing stroke and thromboembolic events in patients with nonvalvular AF, with a significantly lower rate of bleeding events, translating into a reduced 12-month mortality rate (3). Patients with AF undergoing TAVR have a high risk for thromboembolic events and

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bleeding events, demonstrated by high CHA_2DS_2-VASc and HAS-BLED scores. In addition, there is a risk for reduced leaflet motion in patients with aortic valve replacement up to 40% (7) and clinically relevant valve thrombosis. A large multicenter study including 4,266 patients demonstrated clinically apparent valve thrombosis in 0.61% of patients (n = 26) (8). Hence, patients undergoing TAVR might benefit from post-interventional anticoagulation independent of heart rhythm.

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In this study, we evaluated: 1) the impact of AF on outcomes in patients undergoing TAVR compared with those in sinus rhythm; and 2) outcomes in patients with AF treated with apixaban compared with the VKA phenprocoumon.

METHODS

PATIENT SELECTION. Patients were prospectively enrolled and underwent diagnostic evaluation with routine laboratory testing, medical history with current medications, Society of Thoracic Surgeons (STS) score, logistic European System for Cardiac Operative Risk Evaluation score, New York Heart Association functional classification, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. The annual risk for thromboembolic events was calculated using the CHA_2DS_2-VASc score, which incorporates cardiac failure or dysfunction, hypertension, age ≥75 years (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, and sex category (female) (9). The HAS-BLED score, which incorporates hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile international normalized ratio, older age, and drug or alcohol use, was used to evaluate annual risk for bleeding (10). Labile international normalized ratio in patients not exposed to the VKA was set to zero, as this parameter cannot be defined in these patients. Periprocedural complications and 30-day and 12-month clinical outcomes were assessed according to the Valve Academic Research Consortium-2 (VARC-2) criteria (11). The study was approved by the ethics committee of the University of Ulm, and written informed consent was obtained from all patients (NCT02162069).

PROCEDURE. Procedures were performed with local anesthesia under conscious sedation in the hybrid catheterization laboratory. During the TAVR procedure, unfractionated heparin was administered (70 U/kg) after sheath insertion. Anticoagulation was measured by activated clotting time, with repetitive administration of heparin to achieve an activated clotting time of about 250 s. No cerebral embolic protection device was used. For TAVR, the Edwards (Edwards Lifesciences, Irvine, California), Boston Lotus (Boston Scientific, Marlborough, Massachusetts), and Medtronic CoreValve and Evolute (Medtronic, Minneapolis, Minnesota) devices were used. All patients were taking aspirin before the procedure. Clopidogrel was continued when indicated (e.g., after previous coronary stent implantation). In patients with AF, oral anticoagulation with a VKA was discontinued 7 days and oral anticoagulation with a non-VKA 2 days prior to the procedure.

ANTICOAGULATION. Oral anticoagulation was restarted 48 h after TAVR when clinically safe in patients with previous or new-onset AF, as detailed in the study flowchart (Figure 1). Patients with new-onset AF before discharge were switched to oral anticoagulation. Patients were anticoagulated with the VKA phenprocoumon or with apixaban. Apixaban was used beginning in November 2013 in patients with nonvalvular AF at our institution. Oral anticoagulation with apixaban was extended to patients undergoing TAVR with AF at the end of 2014 unless they had severe liver dysfunction or creatinine clearance <15 ml/min. Dose adjustment of apixaban was done according to its instructions for use. Considering the typical TAVR patient with a mean age ≥80 years, all patients were receiving the reduced dose of apixaban (2.5 mg twice daily). Among the 141 patients with AF receiving apixaban, 92 were older than 80 years, 23 had body weight ≤60 kg, 3 had creatinine ≥1.5 g/dl, and 34 were on triple therapy. Patients needing dialysis were receiving a VKA. Patients in sinus rhythm were on single-antiplatelet therapy after the procedure, unless they had undergone previous coronary intervention. After implantation of the Boston Lotus valve, dual-antiplatelet therapy was recommended for 4 weeks. In patients with AF, single-antiplatelet therapy was recommended for 4 weeks in combination with oral anticoagulation. In patients with AF, dual-antiplatelet therapy plus oral anticoagulation was given for 4 weeks after use of the Boston Lotus valve or after previous coronary stenting. Patients were followed up by assessing their clinical histories at scheduled outpatient controls or through telephone contact after 1 and 12 months. At each contact, the same questionnaire (stroke, transient ischemic attack, bleeding, medication, and other

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

NOAC = non-vitamin K antagonist oral anticoagulant agent

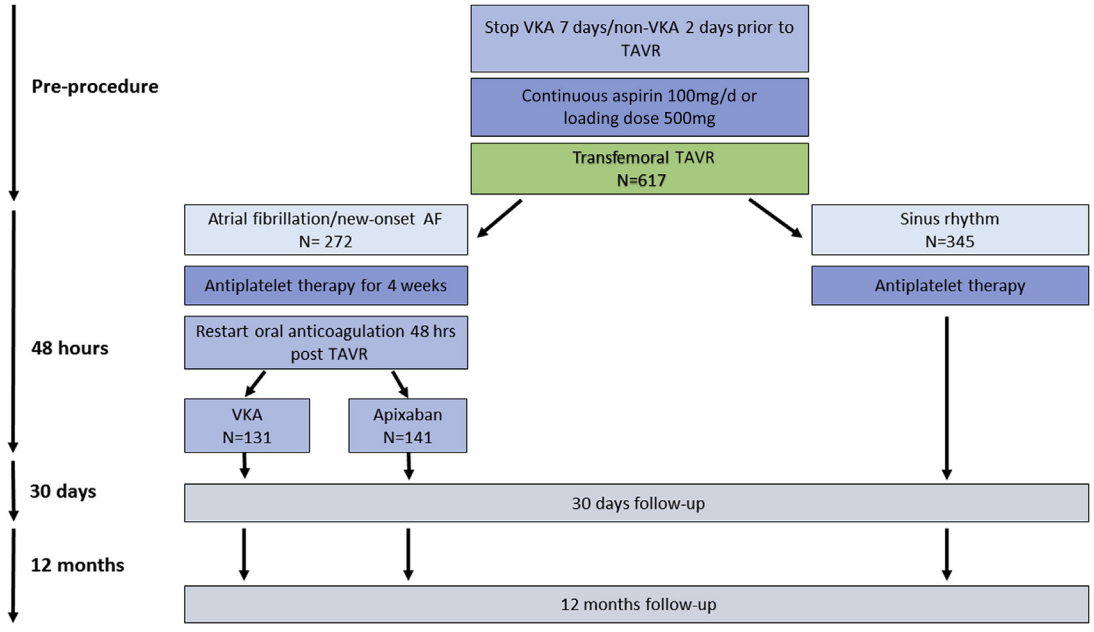
STS = Society of Thoracic Surgeons

TAVR = transfemoral aortic valve replacement

VARC-2 = Valve Academic Research Consortium-2

VKA = vitamin K antagonist

FIGURE 1 Study Flowchart



TAVR = transfemoral aortic valve replacement; VKA = vitamin K antagonist.

complications) was used to ensure adherence to intended anticoagulation regimen.

STATISTICAL ANALYSIS. Categorical parameters are presented as counts and percentages and were compared using the Pearson chi-square test. Continuous variables are presented as mean ± SD. The outcomes of patients in sinus rhythm were compared with those of patients in AF. In addition, we compared the outcomes of patients with AF treated with apixaban or a VKA. Groups were compared using the 2-sample Student *t* test or Mann-Whitney *U* test. Periprocedural, 30-day, and 12-month outcomes were analyzed according to the VARC-2 criteria, including all-cause mortality, major vascular complications, ischemic stroke (disabling and nondisabling), and bleeding complications per Bleeding Academic Research Consortium criteria, including number of red blood cell transfusions and acute kidney injury. Outcomes were analyzed as an intention-to-treat analysis. The early safety endpoint at 30 days was defined according to VARC-2 criteria as a composite of all-cause mortality, all stroke, life-threatening bleeding, acute kidney injury, coronary obstruction, major vascular complications, and valve dysfunction requiring reintervention. The secondary outcome measure was a combination of all-cause mortality and disabling and nondisabling stroke. Events in patients with AF were additionally analyzed for the period >48 h post-TAVR up to 30 days and for the period from day 31 until 12 months to assess the influence of anticoagulation regimen on clinical outcome. This approach eliminates the periprocedural events and covers the period after the start of oral anticoagulation in patients with AF. Landmark analyses were done using Kaplan-Meier estimates and were compared with the log-rank test and Cox proportional regression hazard ratio. Multivariate analyses using stepwise forward regression were performed to evaluate independent predictors for mortality in the total study group and independent predictors for the secondary outcome measure, mortality and stroke, in patients with AF. The following variables were included for multivariate analysis regarding mortality: age, sex, diabetes, renal insufficiency, dual-antiplatelet therapy, STS score for mortality, and AF. The following variables were included for multivariate analysis regarding the secondary outcome measure: age, sex, renal insufficiency, STS score, diabetes, CHA_2DS_2-VASc score, dual-antiplatelet therapy, and anticoagulation regimen. A p value <0.05 was considered to indicate

statistical significance. Statistical analysis was performed using Statistica release 10 (StatSoft, Tulsa, Oklahoma).

RESULTS

OUTCOMES IN PATIENTS IN SINUS RHYTHM COMPARED WITH PATIENTS WITH AF. A total of 617 patients were enrolled. Patients were in sinus rhythm (55.9% [n = 345]) or AF (44.1% [n = 272]). Patients with AF were statistically older (81.3 ± 5.9 years vs. 80.1 ± 6.4 years, p = 0.02) and presented with more comorbidities, as detailed in Table 1. They presented with significantly higher STS and European System for Cardiac Operative Risk Evaluation scores compared with patients in sinus rhythm. Risk for stroke and bleeding per the CHA_2DS_2-VASc (4.9 ± 1.2 vs. 4.7 ± 1.2; p = 0.04) and HAS-BLED (3.1 ± 1.1 vs. 2.7 ± 1.0; p < 0.01) scores was significantly higher in patients with AF, along with a high risk for bleeding, defined by a HAS-BLED score ≥3 (71.3% vs. 47.8%; p < 0.01). Procedural data were similar between groups (Table 1). Pre-dilation was performed in 90.4% versus 93.3% (p = 0.79), and device success was 95.6% versus 92.8% (p = 0.79), respectively. The rate of periprocedural stroke was 3.8% in patients in sinus rhythm and 2.6% (p = 0.42) in patients with AF. There were 2 deaths within 48 h in each group (0.7% vs. 0.6%; p = 0.81). At discharge, 60.0% of patients in sinus rhythm were on dual-antiplatelet therapy, compared with 33.8% of patients with AF (p < 0.01) (Table 1). The rate of new-onset AF was 2.3% at discharge.

The early safety endpoint at 30 days according to VARC-2 criteria was significantly more frequent in patients with AF, 23.2% versus 11.0% (p < 0.01) (Table 2). Patients with AF had significantly higher occurrences of acute kidney injury (5.1% vs. 1.4%, p = 0.01) and life-threatening bleeding (4.4% vs. 0.9%; p < 0.01) at 30 days compared with patients in sinus rhythm. Twelve-month follow-up was available in 285 patients, among whom 154 were in sinus rhythm and 131 in AF (Table 3). All-cause mortality within 12 months was significantly lower in patients in sinus rhythm compared with patients in AF (21.7% vs. 10.1%; p < 0.01). The mortality rate in patients in sinus rhythm was lower within 30 days and in the landmark analysis after 30 days within 12 months (Figure 2). In multivariate analysis, STS score for mortality (p = 0.01) and AF (p = 0.01) were independent predictors of all-cause mortality over 12 months of follow-up. The rate of disabling and nondisabling stroke was similar over 12 months of follow-up, 5.4% and 5.2%, respectively. During follow-up, the combined secondary outcome measure, a composite of

TABLE 1 Baseline Clinical Characteristics and Procedural Data

	Sinus Rhythm (n = 345)	Atrial Fibrillation (n = 272)	p Value
Age, yrs	80.1 ± 6.4	81.3 ± 5.9	0.02
Female	59.5 (197)	40.5 (134)	0.05
BMI, kg/m^2	26.4 ± 4.6	27.1 ± 4.7	0.08
Diabetes mellitus	26.4 (91)	32.4 (88)	0.04
Chronic renal failure	47.1 (113)	52.9 (127)	<0.01
Renal replacement therapy	1.7 (6)	2.9 (8)	0.33
Coronary artery disease	62.3 (215)	62.5 (170)	0.76
History of myocardial infarction	16.5 (57)	19.5 (53)	0.34
History of cardiac surgery	10.7 (37)	12.5 (34)	0.17
Peripheral or cerebral vascular disease	81.2 (280)	85.7 (233)	0.12
History of stroke or intracerebral bleeding	11.0 (38)	12.9 (35)	0.10
Pulmonary disease	51.9 (179)	61.0 (166)	0.22
Permanent pacemaker	9.3 (32)	15.1 (41)	0.09
CHA_2DS_2-VASc score	4.7 ± 1.2	4.9 ± 1.2	0.04
HAS-BLED score	2.7 ± 1.0	3.1 ± 1.1	<0.01
ASA score	3.5 ± 0.6	3.5 ± 0.6	0.60
Logistic EuroSCORE	13.8 ± 12.5	17.4 ± 14.4	0.01
STS score for mortality	6.2 ± 4.6	7.8 ± 5.6	<0.01
Balloon pre-dilation	93.3 (322)	90.4 (246)	0.79
Balloon post-dilation	2.6 (9)	1.5 (4)	0.34
Device success	92.8 (320)	95.6 (260)	0.79
Contrast amount, ml	89.4 ± 36.5	94.7 ± 40.9	0.11
TAVR device implanted			
Boston Lotus	28.7 (99)	23.5 (64)	0.27
Medtronic CoreValve/CoreValve Evolut	16.2 (56)	18.0 (49)	0.62
Edwards XT/Edwards S3	55.1 (190)	58.1 (158)	0.69
Medication at discharge			
Single-antiplatelet therapy	40.0 (138)	66.2 (180)	<0.01
Dual-antiplatelet therapy	60.0 (207)	33.8 (92)	<0.01
Oral anticoagulation	0 (0)	100 (272)	<0.01

Values are mean ± SD or % (n).

ASA = American Society of Anesthesiologists; BMI = body mass index; EuroSCORE = European System for Cardiac Operative Risk Evaluation; STS = society of thoracic surgeons; TAVR = transfemoral aortic valve replacement.

TABLE 2 30-Day Clinical Outcomes

	Sinus Rhythm (n = 345)	Atrial Fibrillation (n = 272)	p Value
Early safety endpoint	11.0 (33)	23.2 (59)	<0.01
Secondary outcome measure	9.7 (14)	20.6 (27)	0.02
All-cause mortality	2.3 (8)	2.6 (7)	0.84
Disabling and nondisabling stroke	4.1 (14)	3.7 (10)	0.82
Intracerebral bleeding	0 (0)	0.4 (1)	0.26
Acute kidney injury stages 2 and 3	1.4 (5)	5.1 (14)	0.01
Life-threatening bleeding	0.9 (3)	4.4 (12)	<0.01
Major vascular complications	3.7 (13)	5.5 (15)	0.32
Valve dysfunction requiring a repeat procedure	0 (0)	0 (0)	–
Endocarditis	0 (0)	0 (0)	–

Values are % (n).

TABLE 3 Late Follow-Up

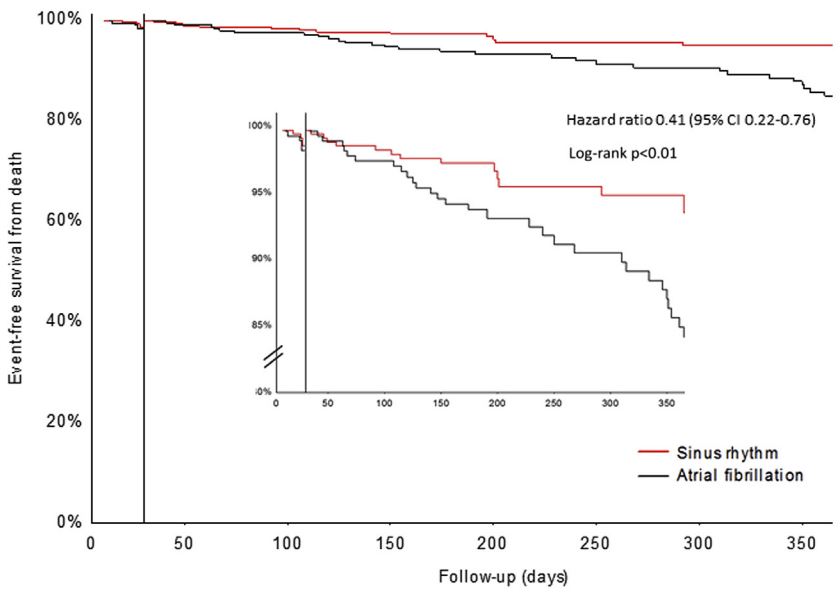
	Sinus Rhythm (n = 154)	Atrial Fibrillation (n = 131)	p Value
Secondary outcome measure*	9.7 (14)	20.6 (27)	0.02
MACE	11.7 (18)	23.7 (31)	0.02
All-cause mortality	7.8 (12)	19.1 (25)	0.01
Disabling and nondisabling stroke	1.3 (2)	1.5 (2)	0.87
Major bleeding	0.6 (1)	0 (0)	0.35
Myocardial infarction	1.3 (2)	0 (0)	0.19
Rehospitalization	11.7 (18)	16.8 (22)	0.28

Values are % (n). *All-cause mortality and all stroke.
MACE = major adverse cardiac event(s).

all-cause mortality and all stroke, was significantly higher in patients with AF, 20.6% compared with 9.7% in patients in sinus rhythm (p = 0.02), whereas the risk for stroke and need for rehospitalization did not differ (Tables 2 and 3).

OUTCOMES IN PATIENTS WITH AF: APIXABAN VERSUS VKA. Among the 272 patients with AF, 141 were treated with apixaban and 131 with a VKA. Baseline characteristics were similar between the groups (Table 4). There were 12 patients with contraindications to apixaban receiving a VKA, 8 patients needing dialysis, 4 patients with severe liver dysfunction, and 19 with creatinine levels >133 μmol/l. At 30-day follow-up, 96.5% of patients in the apixaban group (n = 136) were compliant with the prescribed anticoagulation regimen. Two patients were switched to a VKA for renal impairment, and 3 patients were on antiplatelet therapy only. Among the VKA patients, 87.8% (n = 115) were on a VKA at 30-day follow-up, and 10.7% (n = 14) were switched to a non-VKA anticoagulant. Two patients were on antiplatelet therapy only. The early safety endpoint at 30 days was significantly less frequent in patients treated with apixaban, at 13.5% compared with 30.5% (p < 0.01) (Table 5). There was a significantly lower rate of life-threatening bleeding (3.5% vs. 5.3%; p < 0.01) in patients with AF on apixaban versus a VKA. Looking at the rate of life-threatening bleeding and major vascular complications among patients with AF, none of the patients with life-threatening bleeding on VKA were receiving triple therapy, and only 2 instances of life-threatening bleeding in the apixaban group (1.4%) were in patients on triple therapy (p = 0.17). Also, the rate of major vascular complications was independent of triple therapy in the VKA

FIGURE 2 Landmark Analysis of Mortality



The rate of mortality was lower within 30 days and in the landmark analysis after 30 days within 12 months in patients in sinus rhythm compared with those with atrial fibrillation (log-rank p < 0.01). CI = confidence interval.

and apixaban groups, with 0% of patients in the apixaban group and 1.5% in the VKA group ($p = 0.14$).

There was a numerically lower stroke rate of 2.1% within 30 days in patients on apixaban, compared with 5.3% in patients on a VKA ($p = 0.17$) (**Figure 3**). The secondary outcome measure, a composite of all-cause mortality and all stroke, was similar between patients with AF on apixaban or a VKA (2.1% vs. 3.8%; $p = 0.42$).

During 12-month follow-up, there was no significant difference in stroke rate. During long-term follow-up from day 31 until 12 months post-procedure (**Table 6**), results remained similar for patients on apixaban and a VKA, with no statistically significant difference (1.2% vs. 2%; $p = 0.73$), as shown in the landmark analysis (**Figure 4**). In multivariate analysis, STS score for mortality ($p = 0.03$) was an independent predictor of the combined cardiovascular endpoint of mortality and stroke at 30 days.

TABLE 4 Patients With Atrial Fibrillation: Baseline Clinical Characteristics

	Apixaban (n = 141)	Vitamin K Antagonist (n = 131)	p Value
Age, yrs	82.1 ± 5.3	80.5 ± 6.3	0.20
Female	50.4 (71)	48.1 (63)	0.20
BMI, kg/m^2	27.2 ± 4.2	27.4 ± 5.1	0.72
Diabetes mellitus	32.6 (46)	32.0 (42)	0.16
Chronic renal failure	44.7 (63)	48.9 (64)	0.15
Renal replacement therapy	0 (0)	6.1 (8)	<0.01
Coronary artery disease	66.0 (93)	58.8 (77)	0.86
History of myocardial infarction	17.7 (25)	21.4 (28)	<0.01
History of cardiac surgery	12.8 (18)	12.2 (16)	0.97
Peripheral or cerebral vascular disease	82.9 (117)	88.5 (116)	<0.01
History of stroke or intracerebral bleeding	11.3 (16)	14.5 (19)	0.49
Permanent pacemaker	16.3 (23)	13.7 (18)	0.57
CHA_2DS_2-VASc score	5.0 ± 1.2	4.9 ± 1.1	0.45
HAS-BLED score	3.2 ± 1.1	3.1 ± 1.1	0.66
ASA score	3.6 ± 0.6	3.5 ± 0.7	0.20
Logistic EuroSCORE	18.9 ± 14.5	14.6 ± 13.9	0.05
STS score for mortality	7.5 ± 5.2	7.9 ± 6.3	0.69

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

DISCUSSION

We were able to demonstrate a significant negative impact of AF on clinical outcomes after TAVR within 30 days and 12 months of follow-up. In addition, apixaban was associated with a better early composite safety endpoint compared with a VKA in patients with AF undergoing TAVR.

In the TAVR population, the prevalence of AF is high, ranging from 32.9% in the PARTNER trial (12) to 46.8% in the CoreValve high-risk study (13). The SOURCE XT (Edwards SAPIEN XT Aortic Bioprosthesis Multi-Region Outcome Registry) prospective multicenter registry reported rates of 36.5% pre-existing and 7.2% new-onset AF in 2,706 patients (14). New-onset AF ranges from 1% to about 30% of patients undergoing TAVR, with significantly higher rates after transapical compared with transfemoral access (1,2,12,15). In our patient population, the rate of pre-existing AF was 41.8%, and the rate of new-onset AF was 2.3% within 48 h post-TAVR, triggering the indication for anticoagulation to prevent thromboembolic events in about one-half of patients after TAVR. In patients after cardiac surgery, AF is a well-known independent predictor of stroke, death, and heart failure (16). In patients after TAVR, data on the impact of AF on outcomes are scarce (17-20). We were able to demonstrate in a series of 617 patients a significantly higher early safety endpoint at 30 days according to VARC-2 criteria for patients in AF compared with those in sinus rhythm. In addition, the combined secondary outcome measure, a composite of all-cause mortality and all stroke, as well as the rate of rehospitalization, was significantly more frequent in patients with AF.

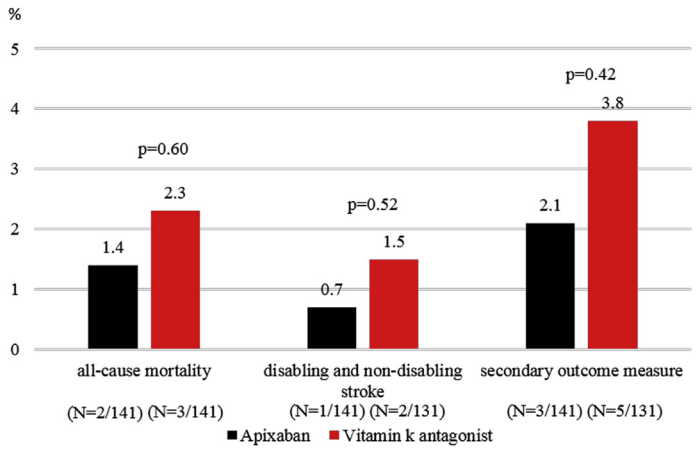
For stroke prevention, NOACs have been approved in patients with nonvalvular AF, showing noninferiority to VKAs in the prevention of thromboembolic events (3-6). In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (3), apixaban has shown superiority to warfarin in patients with AF in preventing thromboembolic events, with a lower rate of bleeding events. Patients with valvular heart disease, however, demonstrated similar results compared with warfarin in a subgroup analysis (21). The existence of valvular

TABLE 5 Patients With Atrial Fibrillation: 30-Day Clinical Outcomes

	Apixaban (n = 141)	Vitamin K Antagonist (n = 131)	p Value
Early safety endpoint	13.5 (19)	30.5 (40)	<0.01
All-cause mortality	1.4 (2)	3.8 (5)	0.22
Disabling and nondisabling stroke	2.1 (3)	5.3 (7)	0.17
Intracerebral bleeding	0.7 (1)	0 (0)	0.34
Acute kidney injury stages 2 and 3	2.1 (3)	8.4 (11)	<0.01
Life-threatening bleeding	3.5 (5)	5.3 (7)	<0.01
Major vascular complications	3.5 (5)	7.6 (10)	0.09
Valve dysfunction requiring a repeat procedure	0 (0)	0 (0)	–
Endocarditis	0 (0)	0 (0)	–

Values are % (n).

FIGURE 3 Short-Term Follow-Up Until 30 Days Post-Procedure



Apixaban was associated with lower rates of all-cause mortality and all stroke compared with a vitamin K antagonist in patients with atrial fibrillation.

heart disease itself is known to be associated with an up to 3.4-fold increase in risk for AF (22).

Considering the high prevalence of AF, oral anticoagulation is a very important issue, especially with respect to the high CHA_2DS_2-VASc scores in these patients. The mean CHA_2DS_2-VASc scores in our patient population were high, at 4.7 ± 1.2 in patients in sinus rhythm and 4.9 ± 1.2 in those with AF ($p = 0.04$), compared with 2.1 in the ARISTOTLE trial (3). Currently, there is no evidence for the use of oral anticoagulation in patients with AF after TAVR, and large randomized controlled trials are unavailable. For surgical mechanical valve implantation, the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement) trial (23) demonstrated a higher rate of thromboembolic events with the use of dabigatran. In surgical bioprosthetic valves, oral anticoagulation for 3 months is broadly recommended because earlier discontinuation was associated with a higher rate of cardiovascular death (24).

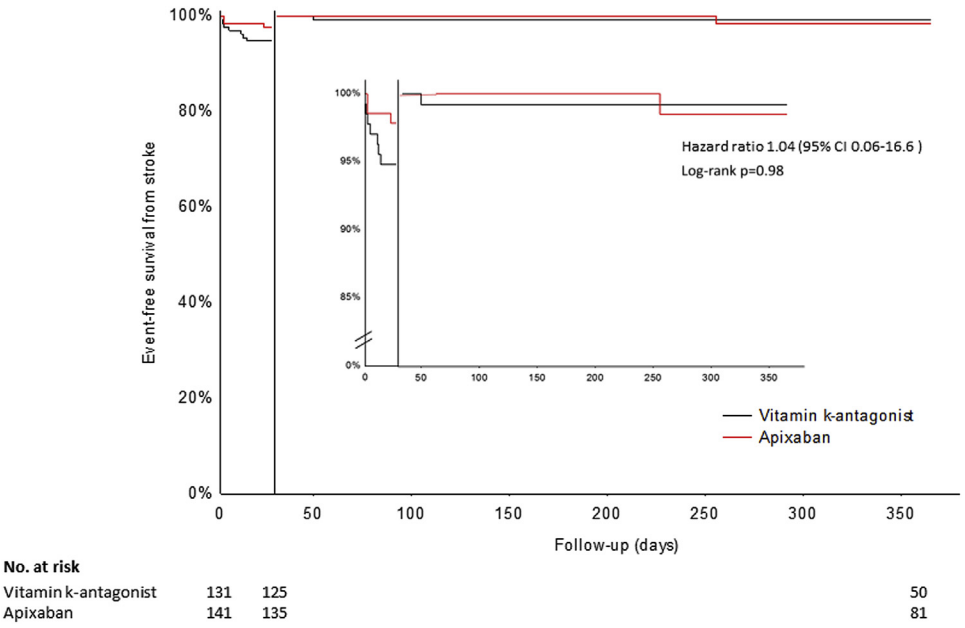
TABLE 6 Patients With Atrial Fibrillation: 12-Month Follow-Up

	Apixaban (n = 81)	Vitamin K Antagonist (n = 50)	p Value
MACE	27.2 (22)	18.0 (9)	0.34
All-cause mortality	23.4 (19)	12.0 (6)	0.18
Disabling and nondisabling stroke	1.2 (1)	2.0 (1)	0.73
Rehospitalization	15.7 (14)	16.0 (8)	0.87
Secondary outcome measure*	24.7 (20)	14 (7)	0.23

Values are % (n). *All-cause mortality and all stroke.
MACE = major adverse cardiac event(s).

In our study, 51.8% of patients with AF were treated with apixaban after TAVR and compared with patients with AF on a VKA, showing a significantly less frequent early safety endpoint at 30 days, driven by significantly lower rates of life-threatening bleeding and acute kidney injury. Corresponding to the results of the ARISTOTLE trial, there was a tendency toward a lower stroke rate with apixaban compared with a VKA at 30 days and 12 months of follow-up. At 30 days of follow-up, patients with AF on oral anticoagulation with a VKA presented with significantly higher rates of acute kidney injury stages 2 and 3 within 30 days of follow-up (2.1% vs. 8.4%; $p < 0.01$). Considering the higher rate of renal dysfunction in the VKA group at baseline, however, this might not be attributable to the anticoagulation regimen only but also to baseline characteristics. In a subgroup analysis of patients on a VKA without dialysis and with creatinine clearance >15 ml/min, results were consistent. Apart from the thromboembolic risk in patients with AF, there is also a considerable risk for bleeding complications after TAVR. Bleeding events are known to have an impact on 30-day and long-term mortality (25). In our older TAVR patient population with mean HAS-BLED scores of 2.7 ± 1.0 in sinus rhythm and 3.1 ± 1.1 in AF, risk for bleeding was high. AF was associated with an increased rate of bleeding events after TAVR, with 4.4% life-threatening bleeding events in patients with AF at 30-day follow-up, compared with 0.9% in patients in sinus rhythm. Consistent with data from the SOURCE XT registry with rates of 7.0% and 6.8% in pre-existing and new-onset AF and 4.8% in sinus rhythm after 12 months of follow-up (14). The rate of life-threatening bleeding complications in our patients with AF was significantly reduced when apixaban was used. Correspondingly, in the ARISTOTLE trial, the annual bleeding rate was reduced to 2.13% in the apixaban group, compared with 3.09% in the warfarin group (3), in patients with nonvalvular AF. In a subgroup analysis of the ARISTOTLE trial in patients with valvular heart disease, the rate of major bleeding was reduced from 6.37% to 4.55% with apixaban compared with warfarin ($p = 0.18$). The use of NOACs, therefore, may reduce bleeding complications in this older patient population at high risk for stroke and bleeding. For bioprosthetic valves, Yadlapati et al. (26) recently demonstrated in a small patient population of 73 patients the safety and efficacy of NOACs in patients with surgical bioprosthetic valves in the prevention of thromboembolic events, but with a higher rate of bleeding. In our population

FIGURE 4 Landmark Analysis of All Stroke



The rate of stroke was similar within 30 days and in the landmark analysis after 30 days within 12 months (log-rank p = 0.98).
CI = confidence interval.

with 617 patients, the rate of disabling and nondisabling stroke was numerically lower in patients with AF on apixaban compared with a VKA with a significantly lower rate of bleeding events. Finally, the unknown risk for reduced leaflet motion and valve thrombosis might be adequately addressed with oral anticoagulation. Hence, patients undergoing TAVR might benefit from post-intervention anticoagulation with a NOAC, not only if in AF.

This is the first study to show safety and efficacy of the NOAC apixaban in patients with AF after TAVR. Larger randomized controlled trials are needed to confirm these findings.

STUDY LIMITATIONS. This was not a randomized controlled trial, though it was a large and the first single-center study comparing apixaban with a VKA in patients with AF after TAVR. The present analysis had all the drawbacks of a registry, in which treatment was open label. Larger randomized controlled trials are needed to confirm these initial exploratory findings.

CONCLUSIONS

In patients undergoing TAVR, AF was associated with significantly higher rates of all-cause mortality, bleeding, and rehospitalization throughout 12 months of follow-up. The early safety endpoint in patients with AF on apixaban was significantly better compared with a VKA.

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PERSPECTIVES

WHAT IS KNOWN? AF is present in up to 40% of patients undergoing TAVR. Currently there is no evidence for the use of oral anticoagulation after TAVR.

WHAT IS NEW? Among patients with AF undergoing TAVR, this is the first study to show that apixaban was associated with a better early composite safety endpoint compared with a VKA.

WHAT IS NEXT? Large randomized controlled trials are needed to confirm these findings.

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