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Research Article

Predictors and Prevalence of Stroke after TAVI Depending on Antithrombotic Therapy

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Abstract

Background: The number of transcatheter aortic-valve implantations (TAVI) is increasing tremendously, whereas the post-procedural antithrombotic management after TAVI is undetermined. Aim of this study is to identify predictors of post-procedural stroke after TAVI with respect to the antithrombotic regimen.

Methods and results: Data from 300 consecutive patients who underwent TAVI at our institution between August 2008 and February 2012 were included in this observational study. The mean age was 82.1 ± 0.3, the logistic EuroScore I was 24.34 ± 0,8. The decision on the post-procedural antithrombotic therapy was left to the operator. From 255 patients that were discharged alive 13 were re-hospitalized due to an ischemic stroke (5.1%). There were no significant differences in the baseline characteristics between patients with stroke and without stroke. In particular diabetes, renal insufficiency, prior cerebral ischemic events, peripheral vascular disease and coronary artery disease were not predictive for the occurrence of strokes. Importantly, the prevalence of atrial fibrillation was 61.5% in the stroke group and 43.4% in the no-stroke group (P=0.19). The CHAD2DS2-VASc scores in the two groups were similar (stroke: 5,68; no-stroke: 5.92). Patients with post-procedural stroke received significantly more often a single antithrombotic therapy (either single antiplatelet or single anticoagulation) than patients without stroke (61.5% vs. 27.3%; P=0.02). In the no-stroke group patients received more often dual antiplatelet therapy (41.3% vs. 15.4%) or a combination of antiplatelet and anticoagulative therapy (27.7% vs. 15.4%).

Conclusion: TAVI patients treated with a combinated antithrombotic therapy may be better protected against stroke than patients with a single antithrombotic therapy.

ABBREVIATIONS

ACC: American College of Cardiology; AF: Atrial Fibrillation; AHA: American Heart Association; ANOVA: Analysis of Variance; AS: Aortic valve Stenosis; AVA: Aortic Valve Area; BMI: Body Mass Index; CABG: Coronary Artery Bypass Graft; CAD: Coronary Artery Disease; CT: Computed Tomography; CVE: Cerebrovascular Events; DAPT: Dual Antiplatelet Therapy; EuroScore: European system for cardiac operative risk evaluation; MACCE: Major Cardiovascular and Cerebrovascular Events; MAPT: Mono Antiplatelet Therapy; NO: Number; NYHA: New York Heart Association; PCI: Percutaneous Coronary Intervention; SEM: Standard Error of the Mean; sPAP: Systolic Pulmonary Artery Pressure; SVAR: Surgical Aortic-Valve Replacement; TAVI: Transcatheter Aortic-Valve Implantation; TIA: Transitory Ischemic Attack; VARC: Valve Academic Research Consortium; VR-4D CT: Four-Dimensional, Volume-Rendered Computed Tomography; Vmax: Peak Aortiv Valve Velocity.

INTRODUCTION

Aortic valve stenosis (AS) is the most prevalent valvular heart disease in the elderly [1]. Transcatheter aortic-valve implantation (TAVI) has been shown to be superior to conservative therapy in inoperable patients with symptomatic severe AS [2] and to be at least not inferior to surgical aortic-valve replacement (SVAR) in patients who are at high risk but suitable candidates for surgery [3,4]. Therefore, TAVI has become the therapy of choice for these patients. By now over 200.000 TAVI procedures have been performed worldwide [5]. TAVI surpassed the annual numbers of isolated SVAR in some countries [6]. However, the benefits associated with the application of TAVI are mitigated by the potential of major, disabling strokes with associated increased mortality and reduced quality of life [7]. The cumulative incidence of cerebrovascular events (CVE) of 8% during a median follow-up of 1 year is concerning, particularly because only clinically overt events were ascertained [8,9]. Noteworthy, almost 50% of

CVE occur later than 24 h after the procedure [8]. Whereas acute CVE (< 1d) are most probably caused by catheter manipulation of the calcified and diseased aortic valve and aortic arch with embolization of calcified debris or thrombotic material, the pathophysiology of subacute (1- 30d) and late CVE (> 30d) is less clear.

This issue becomes even more important since abnormal leaflet motion after TAVI has been reported very recently [10-12]. Four-dimensional, volume-rendered computed tomography (VR-4D CT) scans showed leaflet thickening and impaired leaflet motion in 13-40% of patients after TAVI [12,13]. This was observed in multiple prosthesis types including surgical bioprosthesis. Therapeutic anticoagulation with vitamin-K antagonists, as compared with dual antiplatelet therapy, prevented and effectively treated this phenomenon [10,12]. Moreover, in the pooled cohorts of the RESOLVE and the SAVORY registries, patients with reduced leaflet motion had a higher incidence of stroke or TIA than those with normal leaflet motion [12]. Therefore, abnormal leaflet motion after TAVI is discussed as thromboemolic precursor.

Little evidence is available on optimal antithrombotic strategies after TAVI to prevent strokes. Currently applied regimens are based on non-standardized expert consensus and local clinical practice. Unfractionated heparin during the procedure followed by dual antiplatelet therapy with aspirin (indefinitely) and clopidogrel (1 to 6 months) is the most commonly recommended treatment [10,14]. Among TAVI patients with atrial fibrillation (AF), oral anticoagulation is recommended in accordance with recommendations for AF alone [14]. Whether the addition of antiplatelet therapy to anticoagulation is required in this context remains to be determined.

In the present study, we systematically analyzed predictors and prevalence of post-procedural stroke after TAVI according to the antithrombotic regimen.

MATERIALS AND METHODS

Study population and treatment

Data from 300 consecutive patients who underwent TAVI at our institution between August 2008 and February 2012 were included in this prospective registry. All patients had symptomatic severe aortic stenosis documented by echocardiography according to the American College of Cardiology/American Heart Association's (ACC/AHA) valve guidelines [15]. TAVI was considered for inoperable patients and patients at high risk for surgery. A multidisciplinary "Heart Team" composed of experienced interventional cardiologists and cardiac surgeons determined eligibility for TAVI on the basis of systematic clinical evaluation, angiographic assessment, computed tomography (CT), and echocardiography as suggested by common recommendations [15]. The access route was chosen with respect to diameter, degree of tortuosity, and atheroma of the aortoiliofemoral arterial tree, as assessed by aortoiliofemoral angiography or CT. The following devices were used: Edwards-SAPIEN or SAPIEN XT (Edwards Life sciences, Irvine, California) and Medtronic CoreValve (Medtronic, Minneapolis, MN, USA). TAVI procedures were performed in a hybrid room. Details about the TAVI procedure (transfemoral and transapical) have been extensively explained in previous studies [16-18]. The antithrombotic treatment at discharge was open to the physician's preference. If vitamin-K antagonists were used, target INR values were 2,0-3,0. If a combinated antithrombotic medication was chosen, the duration of the combinated therapy determined for 6 months followed by monotherapy.

Data acquisition

At baseline, patient comorbidities, symptoms, EuroSCORE, echocardiographic characteristics, procedural data and complications were recorded prospectively, following the published recommendations [19]. All patients were followed by regular telephone contacts. Referring cardiologists, general practitioners, other hospitals and patients' families were contacted whenever necessary for further information. Medical documents were acquired to investigate the incidence of major cardiovascular and cerebrovascular events (MACCE) during follow-up according to VARC definitions [19]. We focused our study on subacute and late strokes that occurred after discharge. The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Statistical analysis

Continuous data are expressed as mean ± SEM, unless otherwise stated. Baseline patient characteristics in the two groups (stroke versus no stroke) were compared using one-way analysis of variance (ANOVA) with multiple comparisons (Sidak Test) for continuous variables, and by Chi square tests for nominal variables. If the expected counts were < 5, Fisher's exact test was used. Comparisons of antithrombotic treatment strategies for outcome were done with Chi square tests or Fisher's exact test if the expected outcome was < 5. A two-sided $P< 0.05$ was considered statistically significant. All analysis was performed using Graph pad Prism.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

RESULTS

Baseline characteristics

Mean age was 82.1 ± 0.3 years, 66% were female (Table 1). The Logistic EuroScore I was 24.3 ± 0.8% indicating a high surgical risk. This was determined by a high prevalence of relevant co-morbidities. Coronary artery disease (CAD) was present in 69%, previous coronary artery bypass graft (CABG) surgery in 15%, prior percutaneous coronary intervention (PCI) in 28%, renal insufficiency in 59%, diabetes mellitus in 34%, chronic pulmonary artery disease in 28%, a prior cerebral ischemic event in 14%. All patients had a severe aortic stenosis as indicated by echocardiographic parameters: Vmax 4.1 m/s, mean gradient 43 mmHg, AVA 0,68 mm^2. The mean ejection fraction was 51%, the average systolic pulmonary pressure (sPAP) 46 mmHg. Transfemoral approach was the access route in 142 patients (47%); transapical approach in 158 patients (53%). Within the transfemoral group 114 Edwards Sapien were implanted, 28 Medtronic Corevalve. All transapical devices were Edwards Sapien.

Table 1: Baseline characteristics. The left column represents the total cohort of all patients that were treated with TAVI (n = 300). The next two columns represent the patients that were discharged alive (n = 255) - with or without stroke after discharge during the follow up period. *no* number, *yr* years, *BMI* body mass index, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention, *GFR* glomerular filtration rate, *Vmax* peak aortic valve velocity, *AVA* aortic valve area, *sPAP* systolic pulmonary artery pressure.

Characteristic	Total	No Stroke	Stroke	p value
Total no. of patients	300	242	13	
Male sex - no. (%)	102 (34)	80 (33)	3 (23)	
Female sex - no. (%)	198 (66)	162 (67)	10 (77)	0.55
Age - yr	82.1 ± 0.3	82.4 ± 0.3	81.3 ± 0.5	0.39
BMI - kg/m^2	26.5 ± 0.3	26.4 ± 0.3	26.0 ± 1.0	0.78
Comorbidities				
Atrial fibrillation - no. (%)	113 (38)	105 (43.4)	8 (61.5)	0.19
CAD - no. (%)	206 (68.7)	163 (67.4)	7 (53.8)	0.37
Prior CABG - no. (%)	45 (15.0)	34 (14.0)	3 (23.1)	0.41
Prior PCI - no. (%)	83 (27.7)	63 (26.0)	3 (23.1)	1.00
Peripheral vascular disease - no. (%)	88 (29.3)	68 (28.1)	4 (30.8)	0.76
Prior cerebral ischemic event	41 (13.7)	32 (13.2)	2 (15.4)	0.69
Diabetes	102 (34.0)	74 (30.6)	4 (30.8)	1.00
Chronic obstructive pulmonary disease	84 (28.0)	70 (28.1)	3 (23.1)	0.76
Renal insufficiency				
GFR <60 mL/min	176 (58.7)	136 (56.2)	8 (61.5)	0.78
GFR <30 mL/min	56 (18.7)	36 (14.9)	0 (0)	0.23
Logistic EuroScore I	24.34 ± 0.83	24.5 ± 0.87	20.68 ± 2.29	0.36
Echocardiographic parameters				
Ejection fraction - %	50.8 ± 0.7	51.3 ± 0.7	50.6 ± 2.9	0.83
Vmax - m/s	4.1 ± 0.0	4.1 ± 0.1	4.4 ± 0.2	0.99
Mean Gradient - mmHg	42.5 ± 0.9	43.3 ± 1.0	47.4 ± 4.6	0.44
AVA - mm^2	0.68 ± 0.0	0.67 ± 0.0	0.63 ± 0.1	0.99
sPAP - mmHg	46.0 ± 0.98	45.6 ± 1.1	44.9 ± 3.8	0.99
Procedural parameters				
transfemoral - no. (%)	142 (47)	122 (50.4)	8 (61.5)	0.57
transapical - no. (%)	158 (53)	120 (49.6)	5 (38.5)	0.57

Predictors of ischemic stroke

From 255 patients that were discharged alive 13 (5.1%) were re-hospitalized due to an ischemic stroke. One stroke occurred in the subacute phase (day 2 to day 30) after TAVI, all other strokes occurred late (> 30 days) after TAVI. Comparing the co-morbidities of TAVI patients with and without stroke there were no significant differences. In particular diabetes, renal insufficiency, prior cerebral ischemic events, peripheral vascular disease and coronary artery disease were not predictive for the occurrence of strokes (Table 1). Importantly, the prevalence of atrial fibrillation (AF) was 61.5% in the stroke group and 43.4% in the no-stroke group (P=0.19, (Table 1) and (Figure 1)). However, 88% of the AF patients with stroke received therapeutic anticoagulation, whereas only 71% of the AF patients without stroke. The $CHAD_2DS_2$-VASc scores were high in both groups (stroke: 5,68; no-stroke: 5.92).

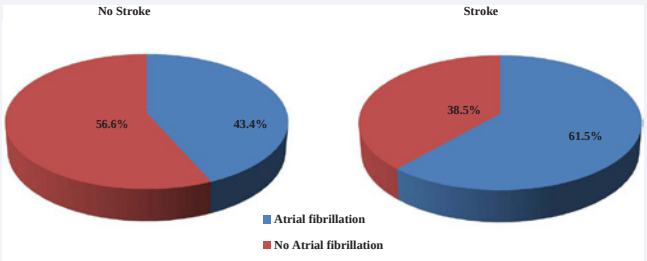

Figure 1 The prevalence of atrial fibrillation (AF) was 61.5% in the stroke group and 43.4% in the no-stroke group.

Impact of antithrombotic medication

The antithrombotic medication at discharge is shown in Figure (2). Within the total cohort 18% of the patients were discharged with a mono antiplatelet (MAPT), 40% with a dual antiplatelet therapy (DAPT; aspirin 100 mg/d plus clopidogrel 75 mg/d). 11% received only anticoagulation, 27% a combination of antiplatelet and anticoagulative therapy. 4% were treated with a triple therapy (DAPT plus anticoagulation). If an anticoagulative medication was used, vitamin-K antagonists (VKA) were the most used substances (exceptions: 1 patient received rivaroxaban, 1 patient received dabigatran, 13 patients received low molecular heparins).

Patients with post-procedural stroke received significantly more often a single antithrombotic therapy (either single antiplatelet or single anticoagulation) than patients without stroke (61.5% vs. 27.3%; P=0.02; (Figure 3A)). In particular, patients treated with single anticoagulative therapy suffered more often from stroke (P=0.02; (Figure 3B)). In the no-stroke

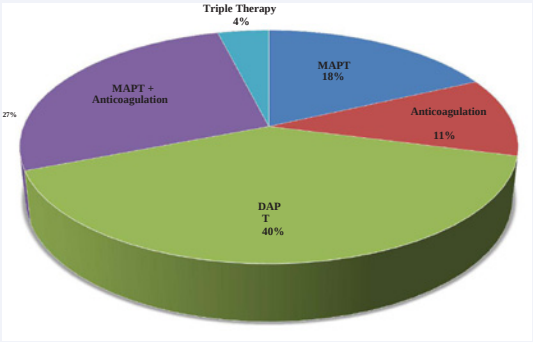

Figure 2 The antithrombotic medication at discharge.

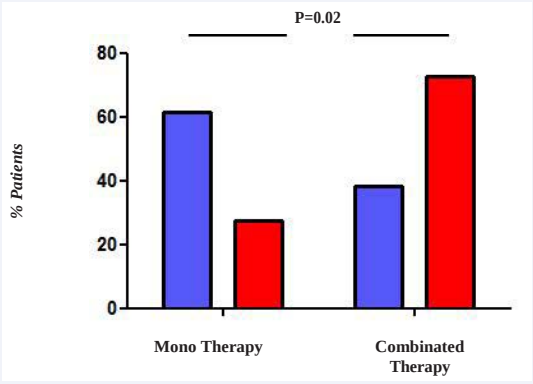

Figure 3a Patients with post-procedural stroke received significantly more often a single antithrombotic therapy.

group patients received more often dual antiplatelet therapy (41.3% vs. 15.4%; P=0.06) or a combination of single antiplatelet and anticoagulation (27.7% vs. 15.4%; P=0.34) or a triple therapy (7.7% vs. 3.7%; P=0.48; (Figure 3B)). (Figure 3C) demonstrates the incidence of stroke in each antithrombotic regimen.

Table (2) displays the time course occurrence of stroke. The median time point of stroke was 284 days after TAVI (range, 16 - 1017 days). Only in 2 patients the antithrombotic medication has changed between discharge and time point of stroke.

DISCUSSION

The pathophysiology and appropriate prevention of post-procedural strokes after TAVI are still unknown. In the present study, the co-morbidities diabetes, renal insufficiency, prior cerebral ischemic events, peripheral vascular disease and coronary artery disease were not predictive for the occurrence of post-procedural strokes after TAVI. The prevalence of AF in TAVI patients was high with high $CHAD_2DS_2$-VASc scores. In patients treated with a single antithrombotic therapy (either single antiplatelet or single anticoagulation) the occurrence of stroke was significantly higher than in patients treated with a combination therapy.

Identifying risk factors for post-procedural strokes after TAVI is crucial to prevent these events in the future. Chronic AF and has been described as an independent predictor of late strokes after TAVI [8,20]. This is consistent with our findings. Even not reaching statistical significance there was a clear trend to a higher prevalence of AF in patients that suffered from stroke after TAVI (61.5% vs. 43.4%). The mean $CHAD_2DS_2$-VASc score was high in both groups (stroke: 5,68; no-stroke: 5.92), which emphasizes the importance of an appropriate antithrombotic treatment in

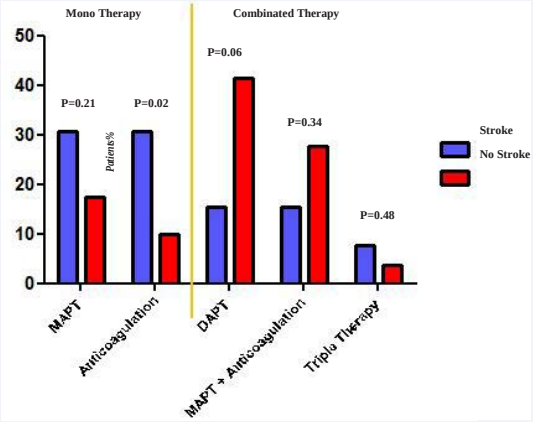

Figure 3b Patients treated with single anticoagulative therapy suffered more often from stroke.

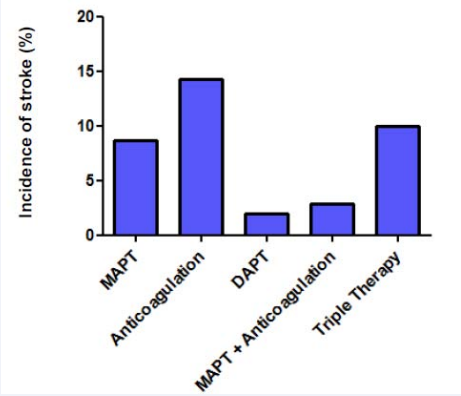

Figure 3c The incidence of stroke in each initial regimen

Table 2: Time course of stroke after TAVI. Medication at discharge and when the stroke occurred.

Patient	Timepoint Stroke (d)	Medication (Discharge)	Medication (Stroke)
1	1017	VKA	VKA
2	41	Aspirin	Aspirin
3	284	VKA+Aspirin	VKA
4	16	VKA	VKA
5	586	VKA	VKA
6	424	VKA+Aspirin	VKA
7	460	VKA	VKA
8	773	Aspirin	Aspirin
9	125	VKA+Aspirin+Clop.	VKA+Aspirin+Clop.
10	86	Aspirin	Aspirin
11	81	Aspirin+Clop.	Aspirin+Clop.
12	56	Aspirin+Clop.	Aspirin+Clop.
13	383	Clop.	Clop.

these patients. However, 88% of the AF patients with stroke received anticoagulation, whereas only 71% of the AF patients without stroke. The $CHAD_2DS_2$-VASc score not only indicates the stroke risk for patients with AF it also displays the cardiovascular co-morbidities of these patients. We were not able to identify any single co-morbidity as significant predictor for post-procedural strokes. In contrast, Nombela-Franco et al. showed that both peripheral vascular disease and prior cerebrovascular disease were predictors for post-procedural strokes [8]. Miller et al. showed that patients with prior stroke and "nontransfemoral candidates" had higher rate of late cerebrovascular events [21]. Bosmans et al., described prior CABG as the only significant predictor for late stroke [20]. Taken together, chronic AF and global atherosclerotic burden seem to increase the risk for late post-procedural stroke after TAVI [22]. However, these are also risk factors for stroke in patients without a prosthetic valve. It has to be assumed that the TAVI prosthesis itself plays a major role. Several factors might contribute to ongoing thrombogenicity of the valve apparatus after implantation, including hemostatic activation due to vessel wall disruption or artificial surface exposure, and flow turbulence through the valve orifice [23]. Since all transcatheter valve systems are stented, exposure of the stent struts to the circulation might trigger initiation of the coagulation cascade and/or platelet activation. The presence of a paravalvular space occupied by the native valve might also be associated with some degree of blood stasis, leading to a prothrombotic environment and resulting risk for thromboembolic events.

Unfortunately, data are lacking to indicate whether cerebral ischemic events after TAVI are primarily due to platelet-based or thrombin-based clot formation. A clearer mechanistic understanding of the pathobiology of thromboembolic events after TAVI will provide a translatable foundation for optimal therapies [24]. Our data suggest that patients treated with a combination of antiplatelet and anticoagulative therapy are better protected against stroke than patients on mono-antiplatelet or mono-anticoagulative therapy, indicating that both pathways are involved in strokes post TAVI. However, patients in our study that were treated with dual antiplatelet therapy were as well protected as patients treated with a combination of antiplatelet and anticoagulative therapy, emphasizing the antiplatelet hypothesis.

Very recently, reduced leaflet motion was noted on VR-4D CT in 13 to 40% of bioprosthetic aortic valves (TAVI and surgical prosthesis) [12]. The prevalence of leaflet motion abnormalities was significant lower among patients who received therapeutic anticoagulation, as compared with those who received either dual antiplatelet therapy or no anticoagulation [10,12]. Moreover, normal leaflet motion recovered in all patients who started or continued to receive therapeutic anticoagulation but persisted in the majority of patients who did not receive anticoagulation [10,12,25]. These observations suggest that the reduced leaflet motion is due to thrombosis supporting the antithrombin hypothesis. In the pooled cohorts of the RESOLVE and the SAVORY registries, patients with reduced leaflet motion had a higher incidence of stroke or TIA than those with normal leaflet motion [12]. These data support the results of our study that an intensive antithrombotic therapy seems desirable. However, the risk of bleeding has also to be considered in this scenario. In patients who had received an surgical aortic valve bioprosthesis, aspirin plus warfarin compared with aspirin only, was associated with reduced risks of death and embolic events, but at the cost of an increased bleeding risk [26]. For TAVI patients this is even more important. TAVI patients are elderly and frail with lots of co-morbidities predisposing for bleeding complications. Late bleeding events (≥ 30 days) after TAVI are frequent and associated with increased mortality [27]. Gastrointestinal, neurological and traumatic bleedings were identified as the most frequent types of late bleeding after TAVI. However, in many TAVI patients receiving blood transfusions no obvious source of bleeding could be identified. Anemia at baseline and AF are independent predictors of late bleeding complications after TAVI [27]. Patients with aortic stenosis may develop a type 2A Von Willebrand syndrome which has been associated with platelet dysfunction and increased risk of bleeding, in particular angiodysplastic gastrointestinal bleeding [28]. Moreover, in older people, antithrombotic therapy is complicated by physiological organ changes, e.g. reduced liver and renal function, and altered body composition and drug distribution [29]. The critical question is whether, in the TAVI patient, the benefits of antithrombotic therapy outweigh the bleeding risks, given those predictors of ischemic and bleeding events co-exists. Measures of frailty are not necessarily the solution, as these, like age, correlate with both ischemic and bleeding events. However, in the present study we did not analyze bleeding events and cannot answer this important question.

The results of our study are in contradiction with recent previous works and meta-analysis. Durand et al., demonstrated that mono antiplatelet (MAPT) as compared with dual antiplateled therapy (DAPT) resulted in less life-threatening and major bleeding whereas the incidence of stroke and myocardial infarction was not different between the 2 groups [30]. Two other studies showed no difference in ischemic and bleeding complications between DAPT and mono antiplatelet therapy after TAVI [31,32]. Moreover, several meta-analyses showed no benefits of DAPT over MAPT in terms of thrombotic events but increased bleeding [33-35]. One recent publication analyzed antithrombotic therapy in 621 patients with AF undergoing TAVI. Patients receiving a combination of anticoagulative and antiplatelet therapy were not better protected against stroke or major adverse cardiovascular events than patients treated with mono-anticagulative therapy with VKA, while increasing the risk of major bleeding [36]. The short follow up period and small sample size in most of these studies precluded to drawing any definitive conclusions regarding efficacy and safety [24].

Our study also has several limitations. We demonstrate a single-center experience with a relatively small sample size. Therefore, the statistical significances in these numbers should be interpreted with caution. The retrospective nature is another obvious limitation of the present study. Moreover, the analysis regarding antithrombotic treatment was not based on randomized treatment, which causes a basic bias of our analysis. Prospective, randomized trials are needed to balance the efficacy and risks of antithrombotic therapy for the vulnerable patients undergoing TAVI. The median time point of stroke in our study was 284 days after TAVI. The combinated antithrombotic therapy

was stopped after 6 months. Therefore, prospective trials should also determine the optimal duration of antithrombotic therapy. The mean $CHAD_2DS_2$-VASc score in our study was high in both groups (> 5,6). This displays the cardiovascular co-morbidities of these patients, which may also contribute to strokes late after TAVI.

CONCLUSION

Ischemic stroke is a devastating and frequent complication after TAVI. The current antithrombotic treatment after TAVI is based on non-standardized expert consensus and local clinical practice. Our data indicate that TAVI patients treated with a combinated antithrombotic therapy (either, dual antiplatelet or antiplatelet plus anticoagulative) may be better protected against stroke than patients with a single antithrombotic therapy. This is of utmost importance and relevance since abnormal leaflet motion after TAVI has been shown very recently and incidence of stroke after TAVI is still a major issue.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the local ethics committee, and written informed consent was obtained from all patients. Ethics approval number: 2214/11.

CONFLICT OF INTEREST

C. Jacobshagen and W. Schillinger received compensation for travel expenses from Edwards Lifesciences, C. Jacobshagen received lecture honoraria from Direct Flow Medical, and W. Schillinger received proctor fees from Edwards Life sciences. All other authors have no conflicts of interest to declare.

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