Clinical Benefit of Direct Oral Anticoagulants Versus Vitamin K Antagonists in Patients with Atrial Fibrillation and Bioprosthetic Heart Valves

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ABSTRACT

Purpose: The use of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) and bioprosthetic heart valve is still controversial. The aim of this study was to compare the tolerability and effectiveness of treatment with DOACs versus vitamin K antagonists (VKAs) in patients with AF and a bioprosthetic heart valve in clinical practice.

Methods: Data for this study were sourced from the multicenter, prospectively maintained AF Research Database (NCT03760874), which includes all patients with AF undergoing follow-up at participating centers through outpatient visits every 3–6 months. The rates of occurrence of thromboembolic events (ischemic stroke, transient ischemic attack, systemic embolism), major bleed, and intracranial hemorrhage (ICH) were assessed. These data were used for quantifying the net clinical benefit (NCB) of DOACs versus VKAs, in accordance with the following formula: (Thromboembolic events incidence rate with VKAs − Thromboembolic events incidence rate with DOACs) − Weighting factor × (ICH rate with DOACs − ICH incidence rate with VKAs). The database was retrospectively queried for patients with AF who were prescribed a DOAC or VKA and had a history of bioprosthetic heart valve replacement.

Findings: A total of 434 patients with AF (DOACs, n = 211; VKAs, n = 223) were identified. Propensity score matching identified 130 patients prescribed DOACs (apixaban, 55.4%; rivaroxaban, 30.0%; dabigatran, 13.1%; edoxaban, 1.4%) and the same number of VKA recipients (warfarin, 89.2%; acenocoumarol, 10.8%). The mean (SD) duration of follow-up was 26.8 (2.3) months. The incidence rates of thromboembolic events were 1.3 per 100 person-years in the DOAC group versus 2.0 per 100 person-years in the VKA group ($P = 0.14$). The incidence rates of major bleed events were 2.6 per 100 person-years in the DOAC group versus 4.9 per 100 person-years in the VKA group ($P = 0.47$). The incidence rates of ICH were 0.38 per 100 person-years in the DOAC group versus 1.16 in the VKA group (hazard ratio = 0.33; 95% CI, 0.05–2.34; $P = 0.3$). A positive NCB of DOACs over VKAs of +1.87 was found.

Implications: According to these data from clinical practice, DOACs seem to be associated with a greater NCB versus VKAs in patients with AF with a bioprosthetic heart valve, primarily due to lower rates of both major bleeds and thromboembolic events. (*Clin Ther*. xxxx;xxx:xxx)

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Key words: atrial fibrillation, bioprosthetic valve, clinical benefit, direct oral anticoagulant, valve repair.

INTRODUCTION

Oral anticoagulation is a therapy effective in reducing the risk for thromboembolism in patients with atrial fibrillation (AF). Currently, direct oral anticoagulants (DOACs) represent the first-line choice in nonvalvular AF,[1] and vitamin K antagonists (VKAs) are the standard of care in patients with AF and a mechanical valve, whereas DOACs are contraindicated in this population.[2,3] The use of DOACs in patients with AF and a bioprosthetic heart valve is still controversial because there is no clear consensus about the definition of *valvular AF* used in the literature or in clinical practice.

Guidelines from the European Society of Cardiology[2] and the European Heart Rhythm Association[4] define *valvular AF* as AF in patients with a mechanical prosthetic heart valve or moderate to severe mitral stenosis, and the use of DOACs in patients with AF and a bioprosthetic valve is considered acceptable.

Recently, a novel functional category, *evaluated heart valves, rheumatic or artificial* (EHRA), in relation to the type of OAC used in patients with AF, was proposed; in particular, *EHRA type 1* refers to a condition in patients with AF and valvular heart disease (VHD) that requires therapy with VKAs, and *EHRA type 2* refers to a condition in patients with AF and VHD eligible for treatment with a DOAC, including patients with mitral valve repair, bioprosthetic valve replacement, and/or transaortic valve intervention.[5] Patients with EHRA type 2 have been included in DOACs studies, which have demonstrated comparable efficacy and tolerability versus warfarin.[5–9]

Contrarily, the American College of Cardiology[10] defines *valvular AF* as AF in the presence of rheumatic mitral stenosis, a mechanical or bioprosthetic, and/or heart valve or mitral valve repair, and does not recommend the use of DOACs in these patients. Few data on the performance of DOACs in patients with AF and a bioprosthetic heart valve in clinical practice are available from the literature,[11,12] and these patients have been relatively represented in randomized clinical trials performed to date.[6,13] The aim of the present study was to compare the tolerability and effectiveness of treatment with DOACs versus VKAs in patients with AF and a bioprosthetic heart valve in clinical practice.

MATERIALS AND METHODS

Database

Data for this study were sourced from the prospectively maintained AF Research Database (NCT03760874), shared by 5 cardiologic centers in Italy (Monaldi Hospital, Naples; University of Campania "Luigi Vanvitelli," Naples; University of Naples Federico II, Naples; Buonconsiglio Hospital, Naples; and Maggiore Hospital, Trieste). The database includes data from all patients with AF followed up at these centers from July 2013 to January 2018 (study period). Follow-up data from outpatient visits every 3–6 months were obtained. During the follow-up visits, clinical status, including the occurrence of stroke, transient ischemic attack (TIA), systemic embolism, major bleed (MB), intracranial hemorrhage (ICH), minor bleed events, and other side effects, was assessed. All patients provided written, informed consent before inclusion in the database, and the local institutional review committee approved the study protocol.

Definitions

For the purposes of this study, the term *thromboembolic events* refers to ischemic stroke, TIA, and peripheral vascular insufficiency. In particular, *ischemic stroke* was defined as a focal neurologic deficit lasting for at least 24 h with no sign of hemorrhage on cerebral imaging and was verified radiologically with cerebral computed tomography on the onset of symptoms and after 48 h. *TIA* was defined as an acute focal neurologic deficit lasting <24 h. Both ischemic stroke and TIA were diagnosed by a neurologist. *Systemic embolism* was defined as an acute vascular insufficiency associated with clinical or radiographic evidence of arterial occlusion and not associated with another likely cause. *MB* was defined as fatal bleeding or symptomatic bleeding in a critical area or organ, or bleeding causing a decrease in hemoglobin level of $\geq$2 g/dL or leading to transfusion of 2 or more units of whole blood or red cells.[14] *Minor bleed* was defined as overt bleeding not meeting the criteria for MB but requiring medical intervention, unscheduled contact (visit or telephone) with a physician, temporary interruption of the use of a study drug

(ie, delayed dosing), pain, or impairment of daily activities.

Patient Population

The database was queried for patients with AF who were prescribed a DOAC or VKA and who had a history of bioprosthetic heart valve replacement. We retrospectively identified 464 patients with nonvalvular AF and a history of bioprosthetic heart valve replacement who received treatment with a DOAC (n = 211) or VKA (n = 253). We excluded patients with a duration of follow-up of ≤360 days from the first qualifying anticoagulant prescription (n = 26) and patients prescribed a VKA with a duration in therapeutic range of <70% (n = 25). Potentially eligible patients receiving a DOAC (n = 200) or VKA (n = 213) were matched by propensity score to generate an analysis cohort with minimal differences in baseline characteristics.

End Points

The primary tolerability outcome was MB. The primary effectiveness outcome was the composite of all events classified as ischemic stroke, TIA, and systemic embolism. The secondary tolerability end point included minor bleeding events. The secondary effectiveness end point included death from any cause.

Statistical Analysis

Descriptive statistics of patient characteristics were carried out; in particular, frequency and percentage for the categorical variables are reported, and means (SD) are used to summarize continuous variables. The incidence of bleeding was calculated both as incidence rate (the ratio between the number of new events that occurred during the follow-up and the person-time accrued from the study members) every 100 patient-years, and as cumulative incidence. Continuous variables were compared using the *t* test, and categorical variables were compared using the χ^2 test. Propensity score matching was used to balance the differences in baseline characteristics between patients receiving DOACs versus VKAs. The model included all pretreatment variables that could possibly have affected treatment assignment and/or outcome, according firstly to clinical judgment and/or previous evidence in literature and, only in the third instance, in case of doubt, considering the results of our exploratory regression analysis for treatment assignment and study end points (less reliable due to risk for overfitting). We performed the nearest-neighbor matching method without replacement and without use of a caliper. This method provided the best compromise between the efficacy of the confounder adjustment, the precision of the estimation, and performance in terms of bias. The ratio of matching was 1:1. The cumulative risk for primary end points over time was estimated using the Kaplan–Meier procedure. A 2-sided *P* value of <0.05 was considered significant for all tests. The net clinical benefit (NCB) was calculated in order to obtain an integrated assessment of the anti-ischemic and prohemorrhagic effects of DOACs versus VKAs, with the following formula: NCB = (Thromboembolic events incidence rate with VKAs − Thromboembolic events incidence rate with DOACs) − Weighting factor × (ICH incidence rate with DOACs − ICH incidence rate with VKAs).[15] The incidence rates of thromboembolic events and MB were calculated as the numbers of events per 100 person-years of follow-up. All statistical analyses were performed using Stata software version 11.1SE (StataCorp, College Station, Texas) and Prism software version 6 (GraphPad Inc, San Diego, California).

RESULTS

Propensity score matching identified 130 DOAC recipients and the same number of VKA recipients who were comparable with respect to demographic and clinical characteristics. INR was not included in propensity score matching because it would have been inherently higher in the VKA group. The baseline characteristics of the study population before and after propensity score matching are summarized in the Table. A total of 434 patients with AF (DOACs, n = 211; VKAs, n = 223) were identified. Propensity score matching identified 130 DOAC recipients (apixaban, 55.4%; rivaroxaban, 30.0%; dabigatran, 13.1%; edoxaban, 1.4%) and the same number of VKA recipients (warfarin, 89.2%; acenocoumarol, 10.8%). The mean (SD) duration of follow-up was 26.8 (2.3) months. DOAC therapy for AF was started at a mean of 964 (497) days after bioprosthetic heart valve implantation.

A total of 8 patients (3 in the DOAC group and 5 in the VKA group) experienced thromboembolic events during follow-up. The cumulative incidences of thromboembolic events in the DOAC and VKA groups were 2.3% and 3.8%, respectively (*P* = 0.47).

Table. Baseline demographic and clinical characteristics of the study population before and after propensity score matching. Data are given as number (%) of patients unless otherwise noted.

Variable	Before Propensity Score Matching			After Propensity Score Matching		
	DOAC (n = 200)	VKA (n = 216)	*P*	DOAC (n = 130)	VKA (n = 130)	*P*
Age, mean (SD), y	64.1 (9.2)	73.3 (6.4)	<0.001	66.1 (8.5)	65.7 (8.9)	0.386
Female	86 (43.0)	87 (40.3)	0.646	56 (43.1)	58 (44.5)	0.918
BMI, mean (SD), kg/m^2	24.8 (5.9)	29.8 (5.2)	<0.001	26.8 (6.1)	27.2 (6.3)	0.251
Clinical parameters, mean (SD)						
CHA_2DS_2VASc score	2.5 (2.2)	3.4 (2.5)	<0.001	3.1 (1.1)	3.2 (1.2)	0.922
HASBLED score	2.4 (1.1)	3.5 (1.5)	<0.001	2.3 (1.2)	2.4 (1.1)	0.720
CrCl, mL/min	71.3 (11.1)	62.5 (12.5)	<0.001	70.3 (21.1)	71.1 (17.2)	0.738
LV EF, %	52.2 (8.5)	44.1 (5.2)	<0.001	54.2 (6.6)	53.1 (5.2)	0.137
Comorbidities						
Hypertension	71 (35.5)	98 (45.4)	0.051	42 (32.3)	43 (33.1)	0.993
Diabetes mellitus	37 (18.5)	61 (28.2)	0.027	27 (20.8)	27 (20.8)	0.886
Heart failure	31 (15.5)	65 (30.1)	0.001	20 (15.4)	21 (16.2)	0.988
Prior stroke/TIA	30 (15.0)	49 (23.1)	0.039	30 (23.1)	33 (25.4)	0.773
Prior MI	17 (8.5)	33 (15.3)	0.048	8 (6.2)	9 (6.9)	0.982
Prior major bleed	9 (4.5)	17 (7.9)	0.220	6 (4.6)	7 (5.4)	0.990
Treatment history						
Bioprosthetic valve*						
Mitral	118 (59.0)	155 (71.7)	0.009	64 (49.2)	68 (52.3)	0.707
Aortic	82 (41.0)	60 (27.8)	0.006	66 (50.8)	62 (47.7)	0.721
Antiplatelet drug	17 (8.5)	33 (15.3)	0.048	8 (6.2)	9 (6.9)	0.982
Study drug						
DOAC						
Apixaban 5 mg	75 (37.5)	—	—	72 (55.4)	—	—
Apixaban 2.5 mg	17 (8.5)	—	—	0	—	—
Rivaroxaban 20 mg	68 (34.0)	—	—	31 (23.8)	—	—
Rivaroxaban 15 mg	20 (10.0)	—	—	8 (6.2)	—	—
Dabigatran 150 mg	20 (10.0)	—	—	17 (13.1)	—	—
Dabigatran 110 mg	7 (3.5)	—	—	0	—	—
Edoxaban 60 mg	2 (1.0)	—	—	2 (1.5)	—	—
Edoxaban 30 mg	1 (0.5)	—	—	0	—	—

Table. (*Continued*)

Variable	Before Propensity Score Matching			After Propensity Score Matching		
	DOAC (n = 200)	VKA (n = 216)	*P*	DOAC (n = 130)	VKA (n = 130)	*P*
VKA						
Warfarin	—	179 (82.9)	—	—	116 (89.2)	—
Acenocoumarol	—	37 (17.1)	—	—	14 (10.8)	—
Dosage						
Therapeutic dosage	168 (84.0)	—	—	130 (100)	—	—
Underdosing	28 (14.0)	—	—	0	—	—
Overdosing	4 (2.0)	—	—	0	—	—

BMI = body mass index; CrCl = creatinine clearance; DOAC = direct oral anticoagulants; LV EF = left ventricle ejection fraction; MI = myocardial infarction; TIA = transient ischemic attack, VKA = Vitamin K antagonists. CHA2DS2VASc and HASBLED are two risk score. CHA_2DS_2 stands for (Congestive heart failure, Hypertension, Age (>65 = 1 point, >75 = 2 points), Diabetes, previous Stroke/transient ischemic attack (2 points). VASc stands for vascular disease (peripheral arterial disease, previous myocardial infarction, aortic atheroma), and sex category (female gender). The HAS-BLED stands for: **H**ypertension **A**bnormal renal and liver function **S**troke **B**leeding **L**abile INR **E**lderly **D**rugs or alcohol.

* Some patients received more than 1 valve.

The incidence rates of thromboembolic events were 1.3 per 100 person-years in the DOAC group versus 2.0 per 100 person-years in the VKA group (hazard ratio = 0.49; 95% CI, 0.19–1.22; $P = 0.14$). A total of 18 patients (6 in the DOAC group and 12 in the VKA group) experienced an MB event. The cumulative incidences of MB in the DOAC and VKA groups were 4.7% and 9.2%, respectively ($P = 0.15$). The incidence rates of bleeding events were 2.6 per 100 person-years in the DOAC group versus 4.9 per 100 person-years in the VKA group (hazard ratio = 0.59; 95% CI; 0.15–2.4; $P = 0.47$).

Among MBs, 4 were ICH (1 in the DOAC group, 3 in the VKA group). The cumulative incidences of ICH in the DOAC and VKA groups were 0.77% and 2.3%, respectively ($P = 0.3$). The incidence rates of ICH were 0.38 per 100 person-years in the DOAC group versus 1.16 in the VKA group (hazard ratio = 0.33; 95% CI, 0.05–2.34; $P = 0.3$). Through these incidence rates we found a positive NCB of DOACs over VKAs, equal to +1.87 (Figure 1).

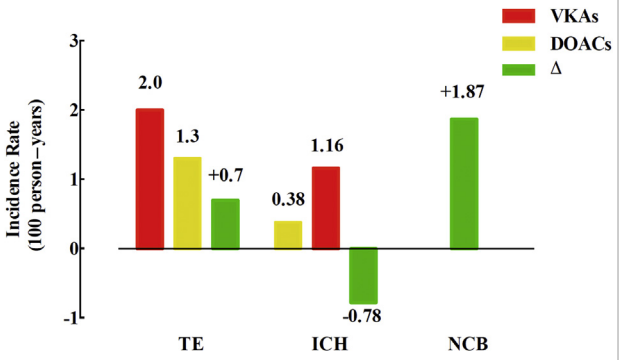

Figure 1. Prevalence rates (100 person-years of thromboembolic events (TE) and major bleeds in recipients of direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs). Differences (Δ) between prevalence rates was used to calculate the net clinical benefit (NCB), with the following formula: TE incidence rate with VKAs − TE incidence rate with DOACs − 1.5 × (ICH prevalence rate with DOACs − ICH prevalence rate with VKAs). ICH = Intracranial hemorrhage.

Figures 2 and 3 show the Kaplan–Meier cumulative probability of MB and thromboembolic events event-free survival, respectively, in the DOAC and VKA treatment groups. A total of 3 patients died during

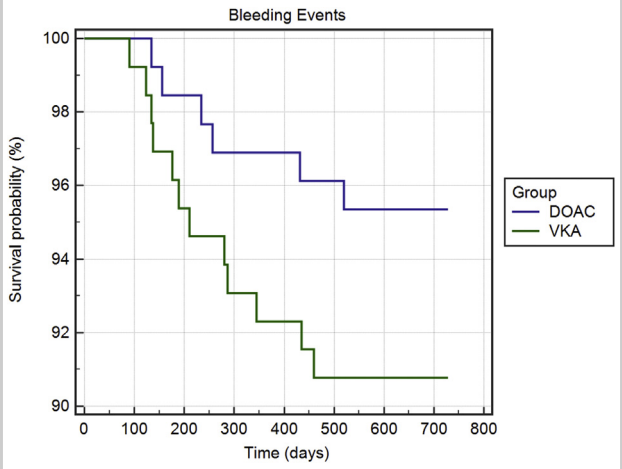

Figure 2. Kaplan–Meier cumulative probability of major bleeding event–free survival in recipients of treatment with direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs).

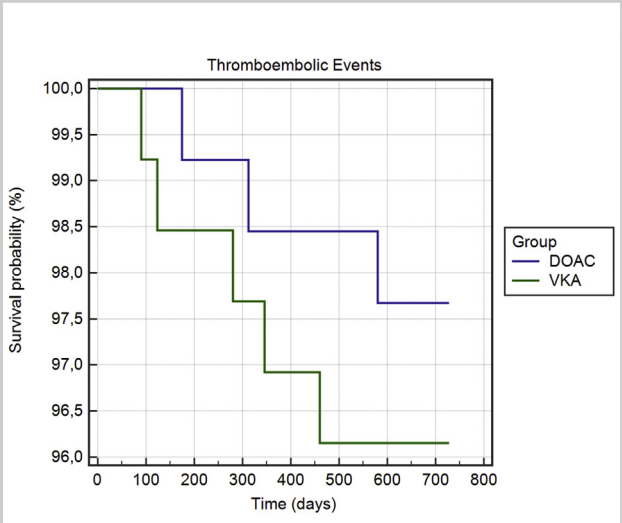

Figure 3. Kaplan–Meier cumulative probability of thromboembolic event-free survival in recipients of treatment with direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs).

follow-up; 2 cardiovascular disease–related deaths (1.5%) occurred in patients receiving a VKA and 1 (0.8%) occurred in the DOAC group ($P = 0.3$). Minor bleeds were reported in 13 of 130 patients (10.0%) in the DOAC group and in 19 of 130 patients (14.6%) in the VKA group ($P = 0.3$).

DISCUSSION

The clinical research on DOAC use for the prevention of thromboembolic complications in patients with AF and a mechanical heart valve was stopped following the results of RE-ALIGN (Randomized, Phase II Study to Evaluate the Tolerability and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement).[16] The trial was terminated prematurely after the enrollment of 252 patients because of excess thromboembolic and bleed events among patients in a dabigatran group.[16] If currently the use of DOACs in patients with AF and a mechanical heart valve is contraindicated, there is some RCT evidence for their efficacy and safer use in patients with AF and a bioprosthetic heart valve.

The findings from the present observational, propensity score–matched, multicenter cohort study suggest that DOACs are associated with improved NCB compared with VKAs among patients with AF and a bioprosthetic heart valve in clinical practice. This finding was driven by reductions in the incidences of MB (~49%) and thromboembolic events (~39.5%) in the study population.

The low cumulative incidence of MBs in the DOAC group (4.6%) compared with that (6.9%) in a previous retrospective study by Yadlapati et al[11] may have been related to the different clinical characteristics of the study population. In particular, the patients in the present study showed a low percentage use of antiplatelet drugs (6.2%) in contrast to those included in the study by Yadlapati et al,[11] which showed a concurrent use of aspirin in the majority of cases (72.6%). It is well appreciated that the use of aspirin in association with OACs is independently associated with a significantly increased risk for bleed compared with use of OACs alone.[17]

The low cumulative incidence of thromboembolic events (2.3%) in the DOAC group in the present study supports the hypothesis that the risk for thromboembolism in patients with AF with a bioprosthetic valve may be similar to that in age-matched patients with AF and conventional stroke risk factors.[18] Our results are in line with the data from ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF)[6] and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in AF-Thrombolysis in Myocardial Infarction 48),[13] the only 2 major clinical trials that have included patients with AF and a bioprosthetic heart valve or valve repair. Patients with AF and VHD had higher risks for thromboembolism and bleeding compared to those who had no VHD, but the relative benefit of apixaban over VKAs with regard to both thromboembolic and bleeding events was preserved.[6] A *post hoc* analysis from the ARISTOTLE trial that included 104 patients (0.6%) with AF and a history of bioprosthetic valve replacement (aortic, n = 73; mitral, n = 26; mitral and aortic, n = 5) and 52 patients (0.3%) with history of valve repair (mitral, n = 50; aortic, n = 2) showed low overall clinical event rates, with no significant differences in any outcomes between apixaban and warfarin.[19]

In the ENGAGE AF trial, 824 patients (13%) with AF had a history of moderate or severe VHD or had undergone prior valve surgery; of these, 191 patients (0.9%) had prior bioprosthetic heart valve implantation (mitral, n = 131 [68.6%]; aortic, n = 60 [31.4%]), and 123 (0.6%) had prior valve repair. Patients with AF and a bioprosthetic valve who were treated with higher-dose edoxaban had similar rates of stroke/systemic embolism and MB compared with those who received warfarin. Patients treated with lower-dose edoxaban had similar rates of stroke/systemic embolism but lower rates of MB compared with those treated with VKAs.[13] The findings from this analysis suggest that edoxaban appears to be a reasonable alternative to warfarin in patients with AF and remote bioprosthetic valve implantation.[13]

In the DAWA (Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively) pilot study,[20] prematurely terminated because of the low enrollment, Duraes et al evaluated the use of dabigatran 110 mg BID versus warfarin in 27 patients with bioprosthetic mitral and/or aortic valve replacement and occurrence of AF postoperatively. The effectiveness of dabigatran appeared to have been similar to that of warfarin in preventing the formation of intracardiac thrombus in this setting.[20]

The clinical impact of an antithrombotic drug should be evaluated using an analysis not only of the anti-

ischemic effect of the treatment, but also its impact on bleed risk. For this reason, Singer et al[15] proposed an integrated approach that combined the anti-ischemic effect with the prohemorrhagic one conferred by anticoagulants. Different types of weighting the hemorrhagic events have been proposed, with the aim of assessing the most likely impact of treatment effect on clinical outcome.[21–23] Given the limited number of events recorded in our population, we opted for the empirically well-validated value of 1.5.[24–26] A better efficacy/tolerability profile of DOACs over VKAs has already been demonstrated in nonvalvular atrial fibrillation patients with AF.[22] Our analysis extends this finding in a clinical practice setting, not well addressed in large-scale trials: patients with AF with a bioprosthetic mitral/aortic valve. These results further confirm the importance of integrating the prevention of thromboembolic events, and tolerability in terms of hemorrhagic complications, when choosing an anticoagulant therapy. In that regard, DOACs not only are a valid alternative in bioprosthetic valve recipients but also perform better than VKAs in terms of NCB.

Limitations

The AF Research Database is a prospectively maintained registry; however, a limitation of the present study was the retrospective nature of the analysis. The small size of the study population and the small number of end point events during the observation period did not permit the performance of a subgroup analysis according to DOACs and bioprosthetic valve type and did not permit adjustment of the weighting factor for hemorrhagic events. None of the patients with AF of the cohort received a DOAC within the first 90 days after bioprosthetic valve implantation.

CONCLUSIONS

Data on the clinical profile of DOACs among patients with AF and a bioprosthetic heart valve in a clinical practice setting are lacking. The findings from this study provide evidence for well-tolerated use of DOACs in this population, justified by a favorable NCB over VKAs. Further prospective studies are necessary to confirm these preliminary observations.

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V. Russo designed the research. A. Carbone wrote the manuscript. E. Attena performed the literature search. A. Rago and C. Mazzone performed the data collection. Proietti and Parisi performed the statistical analysis. Golino, Nigro and D'Onofrio reviewed the manuscript.

CONFLICTS OF INTERESTS

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