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New Oral Anticoagulants Versus Warfarin in Atrial Fibrillation After Early Postoperative Period in Patients With Bioprosthetic Aortic Valve

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ABSTRACT

BACKGROUND The efficacy of novel nonvitamin K antagonist oral anticoagulants (NOACs) in nonvalvular atrial fibrillation (AF) to prevent stroke is well assessed, but NOACs use in AF that occurs after bioprosthetic aortic valve replacement (AVR) is not endorsed. This retrospective real-world study evaluated the efficacy and safety of NOACs prescribed no earlier than 4 months after AVR as an alternative to warfarin in patients with AF.

METHODS We pooled 1032 patients from the databases of 5 centers. Ischemic/embolic events and major bleeding rates were compared between 340 patients assuming NOACs and 692 prescribed warfarin. Propensity score matching was performed to avoid the bias between groups.

RESULTS The NOACs vs warfarin embolic/ischemic rate was 13.5% (46 of 340) vs 22.7% (157 of 692), respectively, (hazard ratio [HR], 0.5; 95% confidence interval [CI], 0.37-0.75; $P < .001$), and the incidence rate was 3.7% vs 6.9% patients/year, respectively (log-rank test $P = .009$). The major bleeding rate was 7.3% (25 of 340) vs 13% (90 of 692) (HR, 0.5; 95% CI, 0.33-0.84; $P = .007$), and the incidence rate was 2% vs 4% patients/year (log-rank test $P = .002$.) After propensity score matching, the NOACs vs warfarin embolic/ischemic rate was 13.1% (42 of 321) vs 21.8% (70 of 321) (HR, 0.6; 95% CI, 0.4-0.9; $P = .02$), and the incidence rate was 4.1% vs 6.7% patients/year (log rank test $P = .01$). The major bleeding rate was 7.8% (25 of /321) vs 13.7% (44 of 321) (HR, 0.5; 95% CI, 0.31-0.86; $P = .01$), and the incidence rate was 2.4% vs 4.2% patients/year (log-rank $P = .01$).

CONCLUSIONS In a real-word study, NOACs use overcomes the indications provided by guidelines. This study evidenced that NOACs use in patients who developed AF after bioprosthetic AVR was more effective in prevention of thromboembolism and safe in reduction of major bleeding events compared with warfarin.

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The recently updated 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines for the management of patients with nonvalvular atrial

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Abbreviations and Acronyms

AF = atrial fibrillation
AVR = Aortic Valve replacement
CI = confidence interval
HR = hazard ratio
NOAC = novel nonvitamin K antagonist oral anticoagulant
OR = odds ratio
PSM = propensity score matching
RCT = randomized controlled trial
TIA = transient ischemic attack
VKA = vitamin K antagonist

fibrillation (AF) recommend oral anticoagulants for the prevention of thromboembolic events in patients with prior stroke, transient ischemic attack, or CHA_2DS_2-VASc* score of 2 or greater (Class I-Level of Evidence A). Between vitamin K antagonists (VKAs) and novel non-VKA oral anticoagulants (NOACs), the choice of NOACs is strongly recommended (Class I-Level of Evidence A).[1-3]

In patients who underwent heart valve replacement, the last American Heart Association/American College of Cardiology Guideline advised against the use of NOACs after mechanical valve replacement and stated that VKAs are the only options for the prevention of thromboembolism.[4] The use of NOACs after valve replacement with a bioprosthesis is not endorsed by major American medical societies guidelines either early after surgical procedure or in patients with postoperative AF.[1,4] By contrast, the 2017 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the management of valvular heart disease state that the use of NOACs should be considered in patients with AF, but not before than 3 months after bioprosthetic aortic valve replacement (AVR).[5] However, this indication was given at Class IIA with Level of Evidence C, reflecting the limited and conflicting evidence that precludes any meaningful conclusions at this time. Nonetheless, in community practice, the use of NOACs overcomes the strict recommendation by guidelines. In the "real world," a significant proportion of patients are prescribed NOACs for stroke prevention in AF that occurs after bioprosthetic AVR, but the safety and efficacy of this choice remain a major concern.

Given this gap in knowledge, the present study was specifically designed to evaluate the safeness and efficacy of NOACs prescribed as an alternative to warfarin in this population of patients.

* C: congestive heart failure or left ventricular systolic dysfunction, 1 point; H: hypertension (blood pressure consistently >140/90 mm Hg or treated hypertension on medication), 1 point; A_2: age ≥75 years, 2 points; D: diabetes mellitus, 1 point; S_2: prior stroke or transient ischemic attack, or thromboembolism, 2 points; V: vascular disease (previous myocardial infarction, peripheral arterial disease, or aortic plaque), 1 point; A: age 65-74 years, 1 point; Sc: sex category (female sex), 1 point.

MATERIAL AND METHODS

This retrospective, multicenter, cohort study analyzed a population of patients who underwent isolated AVR with a bioprosthesis from July 2013 to December 2019. This time frame was related to dabigatran, which was the first NOAC placed on the market.

The choice of biological valve was made in accordance with European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines on the management of valvular heart disease.[6] Wherever not contraindicated, all patients were treated with warfarin for 3 months after AVR for prevention of thromboembolism, with a goal of an international normalized ratio between 2 and 3. Aspirin (75 to 100 mg daily) was given after warfarin was withdrawn.

Patients' data were drawn from the databases of departments that joined the study. All patients who had AVR with a bioprosthesis were identified, and patients who developed postoperative AF were selected. For these patients, we retrieved and stored a number of prespecified definitions. Missing data were completed with relatives, family physicians, or cardiologists who provided their collaboration.

STUDY COHORT. We identified 5067 patients successfully discharged after isolated AVR with a bioprosthesis. Among this population, paroxysmal, permanent, or long-standing persistent AF developed in 1032 patients (20.3%) postoperatively. These patients were prescribed anticoagulant therapy for prevention of thromboembolism and were categorized into 2 groups according to anticoagulation therapy: 340 patients (32.9%) assuming NOACs (NOACs group) and 692 (67.1%) assuming warfarin (warfarin group) (Figure 1). In this series of patients, warfarin was the only VKA used.

The choice of NOACs for thromboembolism prevention was made by cardiac surgeons, cardiologists, or family physicians primarily or after switching the patient from previous warfarin therapy. In accordance with caution determined by results from previous studies, no patients were prescribed NOACs therapy before than 4 months after surgical procedure.[7,8] As a rule, aspirin was withdrawn in all patients who started NOACs or VKAs therapy for AF occurrence. To avoid any misleading interference on end points of interest, all patients treated with combined aspirin and VKA or NOAC were preliminarily excluded.

The NOACs used in our patients were dabigatran (150 mg twice daily), rivaroxaban (20 mg daily), apixaban (5 mg twice daily), or edoxaban (60 mg daily). In patients with impaired renal function, the daily dosage of NOAC was adjusted according with the estimated glomerular filtration rate calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Moderate or severe liver disease was a contraindication for apixaban

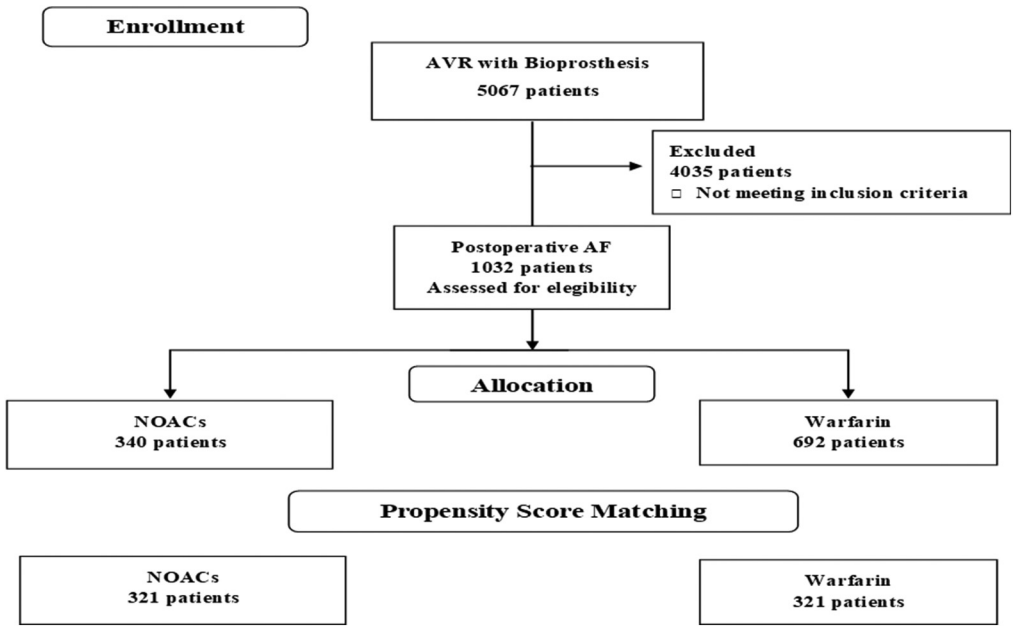

FIGURE 1 Flow diagram of the study population. (AF, atrial fibrillation; AVR, aortic valve replacement; NOACs, novel nonvitamin K antagonist oral anticoagulants.)

and rivaroxaban given their prevalent liver metabolism with cytochrome P450 3A4 involved.

After hospital discharge, regular visits were planned at 1, 3, and every 6 to 8 months in a dedicated outpatient clinic according to standard protocols. Supplemental Table 1 reports the main demographic and clinical characteristic of patients included in the study.

End points were (1) composite, including ischemic events (ischemic stroke, transient ischemic attack, systemic embolism, intracardiac thrombosis), and (2) major bleeding events (intracranial, major intestinal, or urinary bleeding) with NOACs vs warfarin. End points were adjudicated by experienced cardiologists or cardiac surgeons based on data collected. Disagreements were resolved by consensus. Additional information is reported in the Supplemental Material.

The study complies with the 2013 version of the Declaration of Helsinki. Given the retrospective nature of the study, the need for individual patient consent was waived, but all patients had preliminarily granted permission for use of their medical records for research purposes. The University School of Medicine Federico II of Naples Institutional Research Ethics Committee approved the use of databases for research. Given the off-label use of NOACs, patients who received NOACs therapy were informed and provided written consent. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

STATISTICS. Continuous data are presented as mean ± SD and categorical data as proportion. Baseline characteristics between NOACs vs warfarin were compared by *t* test (2-group) for continuous variables and the χ^2 test for categorical or dichotomous variables. The Wilcoxon rank test was used for variables not normally distributed. Data were tested for normal distribution by the Anderson-Darling test.

To eliminate confounding bias due to unequal distribution of risk factors between groups, we performed a propensity score matching (PSM) to generate a subset of matched patients (NOACs vs warfarin) with the same distribution of covariates. A detailed description of the procedure for PSM is reported in the Supplemental Material. At least 321 pairs of patients were successfully matched and compared by means of the nonparametric 2-tailed McNemar test, taking into account the nonindependent nature of matched data.

The cumulative event rate and each event were estimated by the Kaplan-Meier method and compared using the log-rank test. Incidence rates were analyzed as crude incidence of events or as the number of events per 100 persons per year. Weighted Cox proportional hazard

model was used in the prematched or in the 1:1 matched cohort to calculate the risk for events included as single components or cumulative end point of the 2 treatment groups. Data are reported as hazard ratios (HRs) and 95% confidence intervals (CIs).

The validity of the proportional hazard model assumption was assessed by visually inspecting the log-log event curves, and no violation of the assumption was detected. All *P* values were 2-sided, and a value lower than 0.05 was considered statistically significant. Statistical analyses were performed with SAS/STAT 14.3 software (SAS Institute Inc, Cary, NC), or with SPSS 15.0 for Windows (SPSS Inc, Chicago, IL).

RESULTS

In the prematched cohort, several significant differences were present between the groups for demographics and main clinical characteristics, as detailed in Supplemental Table 1. Notably, bleeding risk at the time of AVR was higher in patients from the NOACs group, whereas thrombotic risk was higher in patients from the warfarin group. No patients were preoperatively on AF.

Postoperative AF occurred 28.8 ± 10.4 months after AVR (minimum, 2 days; maximum, 62 months; IQR, 8-39 months). Within the NOACs group, postoperative AF was paroxysmal in 78 patients (22.9%), persistent in 134 (39.4%), and long-standing persistent in 128 (37.6%). Within the warfarin group, paroxysmal AF occurred in 158 patients (22.8%), persistent occurred in 264 (38.1%), and long-standing persistent occurred in 270 (39.1%). The follow-up index, used to measure the follow-up completeness, was 98.2 in the NOACs group and 96.4 in the warfarin group. Cumulative length of follow-up was 1227.5 years in NOACs group and 2218 years in the warfarin group, and mean length of follow-up was 3.8 ± 0.9 years and 4.9 ± 1.4 years, respectively. The NOACs patients were younger, but patients aged older than 80 years were equally distributed. Severe renal dysfunction was more frequent in the warfarin group. The adherence to therapy was of 97.9% in the NOACs group and 98.8% in warfarin group.

Mean time from AVR to start of warfarin was 17.8 ± 7.5 months (range, 0-41 months; median, 21 months; IQR, 10-34 months). There were 55 patients discharged with AF, and AF occurred in the first 3 postoperative months in 39. These patients did not suspended warfarin after AVR.

Notably, NOACs were prescribed off-label in our patients with AF. Mean time from AVR to start of NOACs (given primarily or switched from warfarin) was 26.8 ± 8.2 months (minimum, 5; maximum 40 months; median, 25 months; IQR, 18-33 months). Of 340 patients included in the NOACs group, 183 had crossover from warfarin therapy. Dabigatran was the most frequently prescribed in the first years of the NOACs era, but in the recent era, apixaban and rivaroxaban rapidly exceed dabigatran as a new prescription or as a switch from other NOACs and became the preferred choices. Edoxaban, the last available NOAC, exhibited a strong positive prescription trend after marketing authorization in 2016.

The present study only considered the events that occurred after the initial 4 postoperative months. Postoperative ischemic/embolic events occurred in 46 patients (13.5%) at a mean of 3.4 ± 1.5 years after AVR in the NOACs group and in 157 patients (22.7%) at a mean 3.1 ± 1.2 years after AVR in the warfarin group (HR, 0.5; 95% CI, 0.37-0.75; $P < .001$). The international normalized ratio values of patients at the time of adverse events in warfarin group ranged from 2.2 to 3.3. Linearized major ischemic/embolic events rates were 3.7% patients/year in NOACs group vs 6.9% patients/year in warfarin group. By log-rank test, NOACs therapy was significantly associated with an 0.8-fold reduced risk of ischemic/embolic events compared with warfarin ($P = .002$). Regardless of the study group, approximately 80% of major ischemic/embolic events were anatomically ischemic stroke, approximately 15% involved the lower extremities, and approximately 5% occurred in the upper extremities. Intracardiac thrombosis was founded in a negligible percentage (~1%) of patients.

Major bleeding occurred in 25 patients (7.3%) at a mean of 3.5 ± 1.4 years after AVR in the NOACs group and in 90 patients (13%) at a mean 2.3 ± 1.2 years after AVR in the warfarin group (HR, 0.5; 95% CI, 0.33-0.84; $P = .007$). Major bleeding was intracranial or hemorrhagic stroke in 28% (7 of 25) of NOACs patients and in 33% (30 of 90) of warfarin patients. Linearized major bleeding events rates were 2% patients/year in the NOACs group vs 4% patients/year in the warfarin group. By log-rank test, NOACs therapy was associated with 1-fold reduced risk of major bleeding rates than warfarin ($P = .001$; Figure 2).

After PSM, 321 NOACs patients were successfully 1:1 matched with 321 corresponding warfarin patients (Supplemental Table 2). Cumulative follow-up was 1007.5 years in the NOACs group and 1036 years in the PSM warfarin group. NOACs therapy was confirmed as significantly associated with reduced risk of major ischemic/embolic events compared with warfarin (42 [13.1%] vs 70 [21.8%]; HR, 0.5; 95% CI, 0.35-0.82; $P = .004$). Linearized major ischemic/embolic events rates were 4.1% patients/year in the NOACs group vs 6.7% patients/year in warfarin group. By log-rank test, major ischemic/embolic events were significantly less frequent in the NOACs group than in the warfarin group ($P = .008$). An interesting finding was that intracardiac thrombosis was more frequent in the NOACs group, but

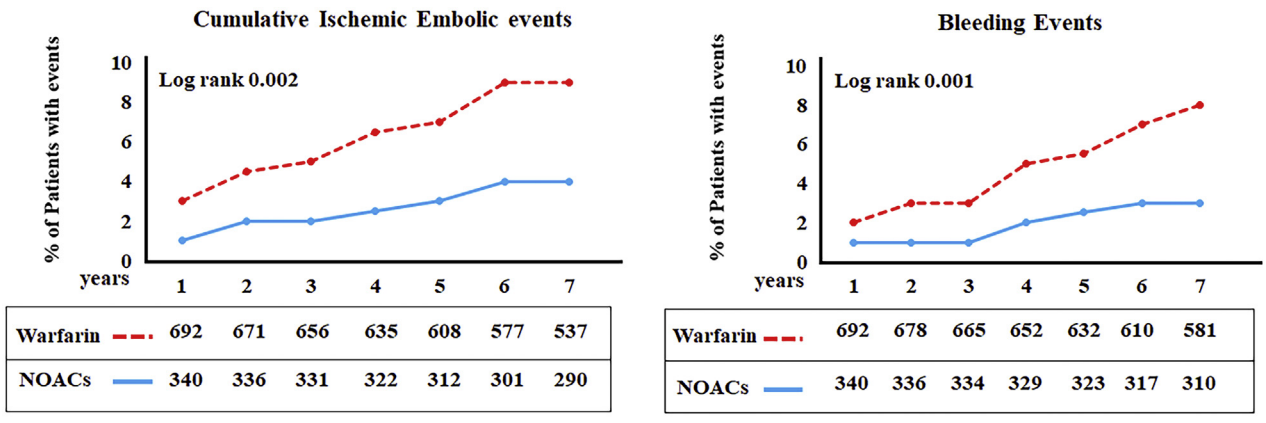

FIGURE 2 Time-to-event curves for composite end points and bleeding before propensity score matching. (NOACs, novel nonvitamin K antagonist oral anticoagulants.)

this event occurred at too low of a rate in both groups to draw any meaningful conclusion.

The use of NOACs was also associated with significantly reduced major bleeding events (22 [6.8%] vs 44 [13.7%]; HR, 0.4; 95% CI, 0.27-0.79; $P = .005$). Linearized major bleeding events rates were 2.1% patients/year in the NOACs group vs 4.2% patients/year in the warfarin group. By log-rank test, major bleeding events were significantly lower in NOACs patients than in warfarin patients ($P = .01$; Figure 3). A recapitulative panel of events is reported in Figure 4.

COMMENT

For many decades, VKAs (mainly warfarin) have been the only oral drug for treatment and prevention of blood clots. Recently, several other medications, known as NOACs, have been studied and released on the market as alternatives to VKAs. Compared with VKAs, NOACs promised a number of hypothetical advantages, consisting of rapid onset of action, shorter half-life, more predictable therapeutic effect, no need for routine monitoring except for periodic assessment of renal function, no need for frequent dose adjustment, fewer potential drug-drug interactions, and no restriction on dietary consumption of food containing vitamin K.

On these bases, 4 pivotal randomized controlled trials (RCTs), including many thousands of patients, have been published in recent years. These RCTs provided robust evidence of the superiority, are at least the noninferiority, of NOACs over warfarin in the prevention of stroke and systemic embolism in patients with nonvalvular AF.[9-12] These results, combined with the

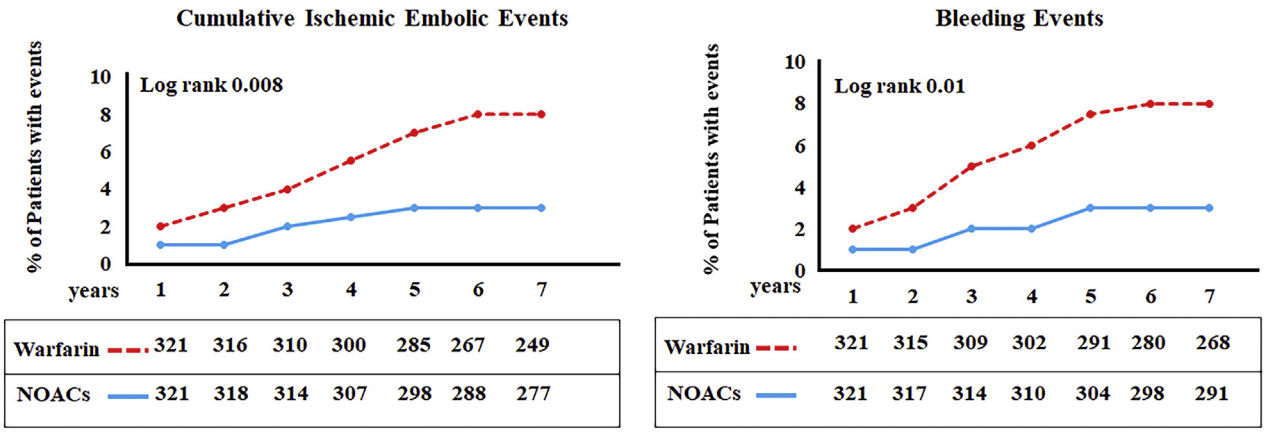

FIGURE 3 Time-to-event curves for composite end points and bleeding after propensity score matching. (NOACs, novel nonvitamin K antagonist oral anticoagulants.)

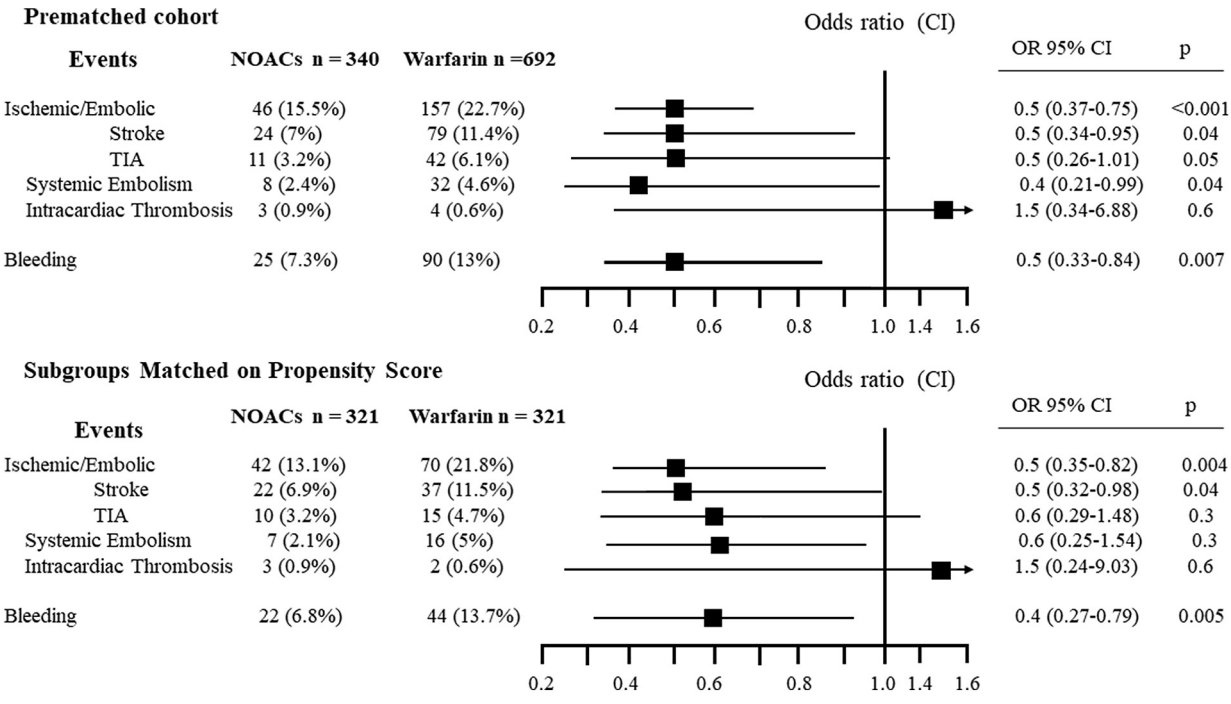

FIGURE 4 Analysis of the end points before and after 1:1 (321 vs 321) propensity score matching. (CI, confidence interval; NOACs, novel non-vitamin K antagonist oral anticoagulants; OR, odds ratio; TIA, transient ischemic attack.)

enhanced safety profile in bleeding risk, supported the inclusion of NOACs in the guidelines of the principal American and European societies as first-line therapy in patients with nonvalvular AF.[1]

The use of NOACs has been also evaluated for prevention of thromboembolism in patients who undergo heart valve replacements. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial tested the possibility to used dabigatran as an alternative to warfarin in patients with mechanical bileaflet valve (aortic, mitral, or both) early after surgical procedure.[7] However, the results were catastrophic for an excess of both thromboembolic and bleeding events among patients receiving dabigatran, which resulted in the statement of the absolute contraindication of NOACs in patients with any type of mechanical valves.

Biological heart valves are considered less thrombogenic compared with mechanical valves but are nonetheless associated with an increased risk of thromboembolic events and require long-term anticoagulation in the setting of concurrent AF. Despite the unfavorable outcomes of the RE-ALIGN trial, there is an increasing growing of interest to investigate the safety and efficacy of NOACs in patients with bioprosthetic valves, but the use of NOACs in patients with AF after bioprosthetic AVR is still a gray zone in clinical practice due to limited investigation. Among the few papers published on this topic, the Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA) Pilot Study evaluated dabigatran vs warfarin in patients with AF that occurred 3 months after bioprosthetic AVR.[8] However, this trial also was terminated prematurely because of a significant drop in recruitment due to the low adherence to the study protocol and the high rate of adverse events in dabigatran group.

By contrast, 2 recent RCTs provided different and more encouraging results supporting the hypothesis that bioprosthetic heart valves should not preclude NOACs use. Of these, the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (interim report) evaluated apixaban as alternative to warfarin in patients with nonvalvular AF. The population processed in this study also included 251 patients with previous heart valve surgery (mitral valve repair and mitral and/or aortic valve replacement with bioprostheses, mechanical valves excluded). The study concluded that apixaban caused fewer bleeding events without a difference in stroke or systemic embolism.[13]

The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, after the analysis of 191 patients with bioprosthetic valves (131 mitral and 60 aortic) treated with edoxaban for AF, evidenced lower rates of stroke and systemic

embolic events and similar rates of bleeding compared with warfarin.[14] However, these results should be taken with caution because both studies analyzed highly heterogeneous subpopulations of patients derived from the respective main trial, and neither study provides any kind of information on the native heart disease, the echocardiographic profile, or describes the procedure performed on heart valves.

The recent meta-analysis by De Souza and colleagues[15] on NOACs vs warfarin used in patients with AF and valvular heart disease analyzed these studies. In large agreement with our results, the authors concluded that NOACs reduce the risk of stroke/systemic embolism and intracranial hemorrhage compared with warfarin in patients with AF and valvular heart disease, with a lower overall risk of major bleeding. However, it should be considered that this meta-analysis focused on the most general (and more heterogeneous) population of the patients with valvular heart disease.

This study presents a large retrospective observational report based on "everyday clinical practice." It was specifically designed for a direct comparison between NOACs and warfarin in patients who developed AF after AVR with a bioprosthesis. The rate of embolic, ischemic, and bleeding events was compared with patients who were assuming warfarin to evaluate the safeness and efficacy of the alternative treatment. To reduce any possible interference due to differences in risk profiles between the groups, all results were further processed after 1:1 PSM. Analyzed in the prematched cohort, our results show that the NOACs group experienced significantly lower event rates of both ischemic/embolic and bleeding events compared with warfarin group. Analyzed as single class of variable, ischemic events occurred at a significantly low rate in the NOACs group whereas, despite tendentially better results in NOACs group, the difference in embolic events did not reached statistical significance between groups.

The analysis after PSM confirmed similar results: compared with warfarin, NOACs significantly reduced the cumulative ischemic/embolic risk by 39.1% and the major bleeding risk by 43.2%. These results could appear contradictory, because no anticoagulant reduces thrombotic risk without simultaneously increasing in bleeding risk. Indeed, some authors report that the risk of major bleeding is increased, at least similarly, in patients who were assuming NOACs compared with warfarin.[9,16] Likely, our results could be ascribed to a more favorable bleeding risk profile after the preliminary exclusion of patients assuming antiplatelet therapy and to the high level of clinical and laboratory surveillance, which is mandatory using newly marketed drugs moreover if prescribed off label. Furthermore, none of our patients received NOACs therapy before 4 months after AVR based on the experience from previous studies reporting that bleeding risk was highly increased when NOACs were given in the first 3 months after surgical procedure. It was striking to note that the use of NOACs after the first introduction on the market resulted in a rapid increase over the years in our cohort from the original 7% to the current 50%.

Finally, literature warns about the lower adherence to NOACs assumption compared with warfarin, which could be an important determinant of thromboembolic events. Lower adherence is usually related to the higher drug cost or to regular coagulation checks not being necessary, which in warfarin patients provides a constant feedback on medication intake. In our cohort, we registered nearly 100% compliance with either NOACs or warfarin, and it was not coincidental. As a rule, all patients who underwent heart valve replacements and their relatives receive detailed formal guidance and continuous reminders from health care providers about the absolute necessity to daily medication adherence and of periodic follow-up. This is moreover possible in our context because all clinical checkups, laboratory monitoring, and drug supplies are completely free.

This study has several limitations. First, are the limitations of retrospective cohort studies. Indeed, an RCT would most appropriate for this comparative evaluation. However, several concerns limit this possibility in our context. At a national level, the use of NOACs is licensed only for nonvalvular AF. The use of NOACs in patients with a bioprosthetic heart valve is not licensed outside the setting of an RCT, but producers are reluctant to assume any responsibility in these trials.

Second, patients on NOACs were switched from warfarin at varying times after AVR, and the reasons behind switching were difficult to track down in our study. Nonetheless, the high number of patients and the large number of variables included in the PSM could largely account for all of the bias factors.

Third, we assumed that every NOAC was taken at the prespecified dose, but we cannot exclude that in daily practice. it could be adjusted in patients with higher bleeding risk or renal/liver dysfunction.

In conclusion, this study suggests that the use of NOACs in the real world overcomes the strict indications provided by guidelines. In daily clinical practice, an increasing number of patients with AF after bioprosthetic AVR assume NOACs for prevention of thromboembolism. Our analysis suggests that the use of NOACs, not given before 4 months after surgical procedure, is more effective than warfarin in the prevention of thromboembolism and is safe for bleeding. However, the therapeutic potential of this family of drugs after bioprosthetic AVR needs further evaluations by specifically designed RCTs

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