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NOAC versus warfarin in the treatment of atrial fibrillation during the first three months after bioprosthetic aortic valve replacement

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Over 4 million heart valve replacement surgeries have been performed in the last 50 years, and it remains the primary treatment for most patients with significant valve disease. The largest group of complications in these patients are thromboembolic events [1].

Atrial fibrillation (AF) occurs in over 42% of patients undergoing aortic valve replacement (AVR), which increases the incidence of embolic complications. The administration of vitamin K antagonists (VKA) is an accepted method of anticoagulant therapy in patients undergoing valve replacement surgery using biological and mechanical prostheses. Recently, a novel 3-month treatment strategy with oral anticoagulants (NOACs) has been approved by the European Society of Cardiology guidelines after bioprosthetic AVR. Reports and guidelines for anticoagulant therapy in the first 3 months after AVR remain inconclusive [2, 3]. However, there are examples of similar studies in the literature. The study aimed to analyze whether NOACs are non-inferior to VKA in preventing thromboembolic events within the first 3 months following bioprosthetic AVR.

Our pilot study had a prospective, randomized, and open-label design. We enrolled 50 patients who underwent bioprosthetic AVR in the Department of Cardiac and Vascular Surgery, with a history of AF in the pre-/postoperative period, regardless of previous anticoagulant therapy. The exclusion criterion was the taking of any medications that could increase the risk of bleeding. Patients were assigned to receive NOAC (n = 25 patients) or warfarin (n = 25 patients) in a 1:1 ratio for the first 3 months after surgery (Table 1).

The study consisted of three evaluations of the patient's condition. The first took place after AVR, on the discharge day, and included blood tests and transthoracic echocardiography (TTE). Patients were also informed about possible adverse events and the study scheme. At 1-month follow-up, telephone contact was made to obtain information about adverse events, i.e., death, bleeding, and thromboembolic incidents. Three months after enrollment, a follow-up visit took place in the hospital. At this appointment, the following were performed: a detailed anamnesis of adverse events, evaluation of the international normalized ratio (INR) levels in patients treated with VKA, a control TTE, and discussion of the further treatment regimen.

The primary feature assessed in the TTE was the function of the bioprosthesis, visualized by

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Table 1. Characteristics of patients stratified by treatment, at baseline, on the discharge day, 1 and 3 months after bioprosthetic aortic valve replacement.

Parameter	All (n = 50)	Warfarin group (n = 25)	NOAC group (n = 25)	P
Baseline characteristic				
Mean age [years]	67.1 ± 7.6	68.2 ± 6.5	65.9 ± 8.6	0.29
Males	27 (54.0)	13 (52.0)	14 (56.0)	0.78
Arterial hypertension	36 (72.0)	20 (80.0)	16 (64.0)	0.21
Coronary artery disease	14 (28.0)	7 (28.0)	7 (28.0)	1.00
Diabetes mellitus	11 (22.0)	4 (16.0)	7 (28.0)	0.31
Previous anticoagulants	13 (26.0)	7 (28.0)	6 (24.0)	0.75
Previous AF	13 (26.0)	7 (28.0)	6 (24.0)	0.75
Previous stroke or thromboembolic incident	1 (2.0)	1 (4.0)	0	0.31
HF with LVEF < 40%	3 (6.0)	2 (8.0)	1 (4.0)	0.55
CHA_2DS_2-VASc scale*	3.0 (2.0–3.0)	3.0 (2.0–3.0)	2.0 (1.0–3.0)	0.27
HAS-BLED scale**	2.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.14
Discharge day				
Creatinine [mg/dL]	0.78 (0.66–0.99)	0.78 (0.65–0.87)	0.77 (0.69–1.00)	0.52
Hemoglobin [g/dL]	9.95 (9.30–10.50)	9.7 (9.1–10.3)	10.0 (9.5–10.8)	0.13
Platelets [$\times 10^9$/L]	206.5 (168.0–247.0)	212.0 (168.0–247.0)	198.0 (177.0–232.0)	0.93
LVEF [%]	60.0 (51.0–60.0)	60.0 (55.0–60.0)	60.0 (50.0–60.0)	0.28
PG_{max} [mmHg]	24.0 (17.0–31.0)	27.0 (17.0–38.0)	23.0 (17.0–26.5)	0.13
PG_{mean} [mmHg]	14.0 (10.0–17.0)	15.0 (10.0–20.0)	13.0 (10.0–15.0)	0.16
V_{max} [m/s]	2.40 (2.04–2.80)	2.60 (2.04–3.07)	2.40 (2.10–2.54)	0.22
VTI_{Ao} [cm]	40.85 (36.25–52.90)	39.4 (35.5–56.1)	40.95 (36.55–51.75)	0.84
VTI_{LVOT} [cm]	20.40 (17.30–23.60	19.2 (17.4–23.0)	21.25 (17.20–24.25)	0.5
Phone contact after 1 month				
Death	1 (2.0)	1 (4.0)	0	0.31
Bleeding	3 (6.0)	3 (12.0)	0	0.07
Follow-up after 3 months				
Death (cumulative)	1 (2.0)	1 (4.0)	0	0.31
Bleeding (cumulative)	3 (6.0)	3 (12.0)	0	0.07
LVEF [%]	60.0 (58.0–63.0)	60.0 (59.0–63.0)	60.0 (56.5–64.0)	0.95
PG_{max} [mmHg]	24.8 (19.0–30.0)	24.0 (18.0–30.0)	26.0 (19.5–30.0)	0.91
PG_{mean} [mmHg]	14.0 (10.0–18.0)	13.0 (10.0–18.0)	15.0 (10.0–18.5)	0.73
V_{max} [m/s]	2.50 (2.22–2.73)	2.47 (2.30–2.73)	2.58 (2.18–2.72)	0.72
VTI_{Ao} [cm]	52.05 (41.75–62.35)	51.7 (42.5–62.3)	52.4 (36.6–62.4)	0.83
VTI_{LVOT} [cm]	24.90 (20.40–27.85)	24.9 (20.1–27.2)	24.4 (20.5–27.9)	0.81

Data are presented as mean ± standard deviation, median (interquartile range), or counts (percentages).
*CHA_2DS_2-VASc scale scores reflect the risk of stroke, with values ranging from 0 to 9, and with higher scores indicating greater risk.
**HAS-BLED scale scores reflect the risk of major bleeding among patients with AF who receive anticoagulant therapy, with values ranging from 0 to 9, and with higher scores indicating greater risk.
AF — atrial fibrillation; AVR — aortic valve replacement; HF — heart failure; LVEF — left ventricular ejection fraction; PG_{max} — peak aortic valve pressure gradient; PG_{mean} — mean aortic valve pressure gradient; V_{max} — peak aortic valve velocity; VTI_{Ao} — aortic velocity time integral; VTI_{LVOT} — left ventricular outflow tract velocity time integral

standard echocardiographic parameters, i.e., peak aortic valve pressure gradient (PG_{max}), mean aortic valve pressure gradient (PG_{mean}), peak aortic valve velocity (V_{max}), aortic velocity time integral (VTI_{Ao}), left ventricular outflow tract velocity time integral (VTI_{LVOT}), the overall function of the left ventricle (left ventricular ejection fraction), and the possible amount of fluid in the pericardial sac.

The factor Xa inhibitor apixaban was selected as an anticoagulant drug in the NOAC group. All patients received the same drug at a dose of 5 mg twice daily, unless there were indications for a reduced dose of 2.5 mg twice daily (creatinine clearance 15–29 mL/min or two of the following: age ≥ 80 years, weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL).

The study was approved by the local independent bioethical committee and complied with the Declaration of Helsinki. Written informed consent was obtained from all included patients.

Based on preliminary data, descriptive characteristics were performed for each group. Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as counts (percentages). A t-test or a Mann-Whitney U test was used to compare the continuous variables. Categorical variables were compared using a χ^2 test. P-values < 0.05 were considered statistically significant. Statistical analysis was performed in Statistica 13.3 (StatSoft, TIBCO Software Inc.).

Three (12%) patients in the warfarin group and none in the apixaban group had a major bleeding incident. Two of them had pericardial effusion, and one had pleural effusion. All 3 patients required hospitalization to perform drainage. One (4%) death was reported in the warfarin group and none in the apixaban group. The patient died in hospital 9 days after surgery due to massive pericardial bleeding, probably from heart wall rapture, while adjusting the therapeutic INR. One patient was lost to follow-up.

After 3 months, 60% of patients in the warfarin group decided to change the anticoagulant treatment on NOAC, mainly due to labile INR. In both groups, there were no bioprosthesis dysfunction findings in the thromboembolic mechanism. We have decided to continue our study by an escalation of the enrollment group.

There is a deficiency of clinical data comparing NOAC and warfarin in the anticoagulant treatment of AF during the first 3 months after bioprosthetic AVR. Most trials evaluating NOAC vs. warfarin have a heterogeneous group of patients considering different types of valvular heart disease (native valve diseases, bioprosthetic and mechanical valves) or anticoagulation treatment applied > 3 months postoperatively [4]. The RIVER trial had the most similar model to our study. In this randomized, controlled trial, 1005 patients were enrolled to assess the efficacy and safety of NOAC (rivaroxaban) compared with warfarin in patients after bioprosthetic mitral valve replacement (MVR). However, only 189 patients were randomized up to 3 months after MVR. In this subgroup, the incidence of primary outcome composed of death, major cardiovascular events, or major bleeding after 12 months was 6.4% in the rivaroxaban group and 18.9% in the warfarin group. Rivaroxaban was non-inferior to warfarin in patients with AF and bioprosthetic mitral valve [5].

The results of the RIVER trial support our study findings on the efficacy of NOAC compared to warfarin in patients with AF after surgical valve replacement with a bioprosthesis. There may also be a potential legitimacy for prescribing chronic anticoagulation in postoperative AF due to the high safety of NOAC, although 44% of the subjects were women, and the mean CHA_2DS_2-VASc score was 2. However, further prospective studies on a larger population are required to assess the efficacy and safety of NOACs in patients with AF and recent (< 3 months) bioprosthetic AVR.

In conclusion, in patients with AF during the first 3 months after bioprosthetic AVR apixaban was non-inferior to warfarin for thromboembolic events. Also, apixaban seemed to have a better safety profile than warfarin for the incidence of death or major bleeding.

Conflict of interest: None declared

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