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Early anti-coagulation therapy in new-onset atrial fibrillation after coronary artery bypass grafting: a randomized trial pilot study

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Abstract

Background New-onset postoperative atrial fibrillation (POAF) is a common complication after coronary artery bypass grafting (CABG) surgery, increasing the risk of embolism and stroke. There is a lack of information on the use of anticoagulants in this context. The choice between Warfarin and Direct oral anticoagulants (DOACs) also is not well-established. This randomized study aimed to compare the feasibility and safety of Warfarin and Rivaroxaban in preventing thrombotic events in POAF patients after isolated CABG.

Methods A total of 66 patients were randomized parallelly with 1:1 allocation to receive either Rivaroxaban ($n=34$) or Warfarin ($n=32$). Major bleeding events within 30 days after discharge were the primary outcome. Secondary outcomes included minor bleeding events and thrombotic episodes. Clinical characteristics, medication regimens, and left atrial diameter were assessed. Statistical analyses were performed using appropriate tests.

Results No thrombotic episodes were observed in either treatment arm. No major bleeding events occurred in either group. Four minor bleeding events were reported, with no significant difference between the treatment groups ($P=0.6$). Patients with atrial fibrillation had significantly larger left atrial diameters compared to those with normal sinus rhythm (40.5 vs. 37.8 mm, $P=0.01$).

Conclusions This pilot study suggests that Warfarin and Rivaroxaban are both safe and effective for preventing thrombotic episodes in POAF patients after isolated CABG. No significant differences in major bleeding events were observed between the two anticoagulants. These findings may support the preference for DOACs like Rivaroxaban due to their convenience and easier maintenance.

Trial registration Number IRCT20200304046696N1, Date 18/03/2020 https//irct.behdasht.gov.ir/.

Keywords Coronary artery bypass grafting, Atrial fibrillation, Embolism and thrombosis, Bleeding, Warfarin, Rivaroxaban

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Introduction

New-onset postoperative atrial fibrillation (POAF) is one of the most common complications after coronary artery bypass grafting (CABG) that affects approximately 15–40% of patients after surgery [1–3]. POAF has a negative prognostic impact as patients with atrial fibrillation (AF) have an increased risk and incidence of embolism, with a 4- to 5-fold higher risk of ischemic stroke [4, 5].

Surgical procedures, particularly cardiac surgery with cardiopulmonary bypass (CPB), trigger a systemic inflammatory response that plays a significant role in the development of POAF. CPB induces the release of pro-inflammatory cytokines like interleukin-8 (IL-8) and tumor necrosis factor (TNF), which can lead to various postoperative complications. Oxidative stress, resulting from the uncontrolled production of reactive oxygen species (ROS), is also implicated in post-cardiac-surgery AF, exacerbated by factors such as preexisting diseases, blood transfusions, and reperfusion injury. Disruption of the pericardial membrane during surgery contributes to electromechanical disturbances that promote AF. Additionally, electrolyte imbalances like hypomagnesemia and hypokalemia commonly observed in the perioperative period can further increase the risk of AF. These multifaceted mechanisms underscore the complex interplay of inflammatory and oxidative pathways in the pathogenesis of POAF following cardiac surgery [6].

Traditionally, anticoagulation therapy in patients with AF, considering the CHA2DS2-VASc scoring tool, has been recommended. However, there is a lack of sufficient data on the occurrence of AF after cardiac surgeries. There are several controversial issues in the approach to POAF, including: (1) Should anticoagulation be considered for only high-risk POAF patients or all patients regardless of their risk?, (2) Are traditional scoring tools also appropriate for the POAF setting?, (3) How long should a POAF episode last to be eligible for anticoagulation treatment?, (4) How long should the anticoagulation therapy be continued in these patients?, (5) Which one is the better choice for treatment? Vitamin K antagonists (VKA) or Direct oral anticoagulants (DOACs) [7].

Current guidelines suggest an oral anticoagulant treatment for POAF episodes lasting over 48 h and to continue at least four weeks after conversion to sinus rhythm [8–11].

Warfarin, a VKA, functions by blocking the vitamin K-epoxide reductase, hindering coagulation steps involving vitamin K-dependent clotting factors, namely factors II, VII, IX, and X. On the other hand, Rivaroxaban, a factor Xa inhibitor, directly binds to the active site of factor Xa, inhibiting both free and clot-associated forms of the factor. Both types of anticoagulants are common drugs of choice for preventing thrombotic events in patients experiencing AF [12–14].

Based on the current literature, the efficacies of these two agents are comparable [5]; however, because of the convenience of the direct factor Xa inhibitors, clinicians tend to prefer these newer agents. There is however another issue that has been raised on several occasions, that management of toxicity in Warfarin is simpler, and direct factor Xa inhibitors are harder to reverse once bleeding events occur. A major challenge surrounding this issue is that most of the studies in this area are observational and retrospective. That's why we designed a randomized prospective trial to deliver a more accurate representation and comparison of these two pharmacological agents.

Methods

This is a two-arm parallel group 1:1 block randomized controlled trial, investigating the feasibility and safety of utilization of DOACs vs. VKAs in patients with atrial fibrillation after isolated CABG. The study was conducted in a major academic tertiary care hospital, specializing in the treatment of cardiovascular disorders and a wide range of research projects, Tehran Heart Center, at Tehran University of Medical Sciences [15], from April 2020 to November 2022 (Six months: Enrollment, Eligibility screen, Informed consent obtainment, and Allocation, One month: Follow-up). We included patients from cardiac surgery wards and intensive care units who had events of AF, lasting more than 48 h without a previous history of AF. We excluded patients with active bleeding, history of allergy to trial medications (including Heparin, Warfarin, and Rivaroxaban), moderate to severe mitral stenosis, history of stroke during admission or up to one month before surgery, history of pregnancy up to 1 year before the study, reproductive-age women not using reliable contraception, patients already under treatment with anticoagulants for other medical reasons, patients with glomerular filtration rate (GFR) less than 30 ml/min/1.73 m^2, and those with International Normalized Ratio (INR) more than 1.7. The attending physician (cardiologist) enrolled participants and assigned them to interventions.

We used the "HAS-BLED" score for the risk of major bleeding [16], and those who scored high risk for bleeding on this scale were started on these treatments diligently and with more frequent follow-ups (as the routine procedure for those with high scores of HAS-BLED). We also calculated patients' GFR based on the Cockcroft formula [17], those with GFR ranging between 30 and 50 ml/min/1.73 m^2, received 15 mg of Rivaroxaban, and those with GFR above 50 ml/min/1.73 m^2, received 20 mg per day. In the Rivaroxaban (sourced from Actover Co.) group, patients were started on treatment after 48 h and in the first 72 h, which was continued for 4 weeks. In the other arm, the patients were started on Heparin in the first 12 h, which was continued for at least 5 days, 4 of

which had to have overlap with Warfarin (Sourced from Crescent Pharma). The heparin was continued for 2 more days after reaching the desired INR of 2–3. Heparin was then discontinued, and Warfarin was administered for 4 weeks. We followed the patients weekly after discharge to ensure an INR of 2–3.

We defined the primary outcome as any major bleeding in the first 30 days after discharge. Major bleeding was defined as bleeding events requiring another surgery, invasive procedures such as endoscopy or cystoscopy, intracranial hemorrhage (confirmed by computed tomography or magnetic resonance imaging), or events requiring an infusion of more than 2 units of packed cells. Secondary outcomes included minor bleeding events and thrombotic episodes.

Since there are controversies regarding the sample size of feasibility studies [18–20] and no exact and universal formula exists, we decided to include and randomize among all the patients we had available at the time with the conditions as explained before. We expected to have around 70 patients in this duration. After obtaining a sufficient sample size for the pilot phase, permuted block randomization was conducted using random allocation software. This method involved the creation of variable block sizes to prevent predictability and maintain the element of randomness in the assignment process. Subsequently, a total of 34 patients were randomly allocated to the Rivaroxaban group, while 32 patients were assigned to the warfarin group.

Due to the divergent aftercare requirements associated with the two drugs under investigation, blinding both participants and healthcare providers to the assigned treatment was not feasible in this study. The distinct post-treatment protocols, including monitoring procedures, dosage adjustments, and potential adverse event management, necessitated transparency regarding the allocated intervention for effective patient care and safety. Consequently, the inherent differences in the management of patients receiving Rivaroxaban versus Warfarin precluded the implementation of blinding strategies to conceal treatment allocation. The CONSORT diagram is depicted in Fig. 1.

Informed consent was obtained from each patient before recruitment and the study protocol was reviewed and approved by the ethical committees of the Tehran University of Medical Sciences with the code of: "IR.TUMS.MEDICINE.REC.1398.836". The trial was also registered in IRCT with code "IRCT20200304046696N1" on 18/03/2020. The data was analyzed using SPSS version 26. Because this is a feasibility study, we were not looking to make too many statistical comparisons in our data; however, we used Fisher's Exact, Mann-Whitney U, and Kendall's Tau test where appropriate.

Results

Six hundred forty-three patients undergoing isolated CABG at our institute were assessed for eligibility for inclusion during the study period. Episodes of POAF occurred in 98 patients; of them, 79 subjects experienced the first episodes consistent with the AF duration in our inclusion criteria. Three and two of them were on anticoagulant medication because of a history of deep venous thrombosis and left ventricular clots, respectively. A cerebrovascular accident (CVA) occurred in one of the patients during admission and before anticoagulation therapy. Two of them were excluded due to GFR of less than 30 ml/min/1.73 m^2 and 5 patients declined to participate. A total of 66 patients with a mean age of 68.23 (SD = 6.56) years experiencing POAF were included in the study and randomized into two groups receiving either Rivaroxaban (n = 34) or Warfarin (n = 32). All the patients in the Warfarin group received bridge therapy with Heparin. During discharge, we ensured that all patients were within the therapeutic INR range of 2 to 3 while on VKA therapy. However, during subsequent visits, 8 patients were found to have slightly out-of-range INR, and their medication doses were adjusted to bring them back into the therapeutic range during follow-up visits.

One of the patients in the DOACs group received Rivaroxaban 15 mg because of GFR 30–50 ml/min/1.73 m^2 and the others received Rivaroxaban 20 mg. The main clinical characteristics of the patients are outlined in Table 1. As indicated in the table, most baseline characteristics did not differ significantly among the two groups; however, the group receiving Rivaroxaban was significantly younger and tended to be administered Clopidogrel more than Aspirin. The two groups were also different regarding relevant cardiovascular comorbidities; the prevalence of hypertension and dyslipidemia were higher in the group receiving Rivaroxaban.

In the duration of patients receiving anticoagulation therapy at the hospital and up until 30 days after discharge, none of the patients experienced major bleeding events, in either group. A total of 4 minor bleeding events occurred, but the difference in incidence was ultimately not significant among the two treatment groups (Table 2). The isolated hematoma was a case of cutaneous hematoma in the arm, very similar to a previous case report in a Warfarin-treated patient [21].

The 3 bleeding events in the Rivaroxaban arm were receiving simultaneous Aspirin (n = 1) or Clopidogrel therapy (n = 2), while the single bleeding event in the Warfarin arm was undergoing triple therapy. The type of each minor bleeding event is described in Table 3. Furthermore, it is notable that both treatments were comparably successful in preventing thrombotic episodes, as no patients in either group suffered episodes of transient ischemic attack, CVA, or pulmonary thromboembolism.

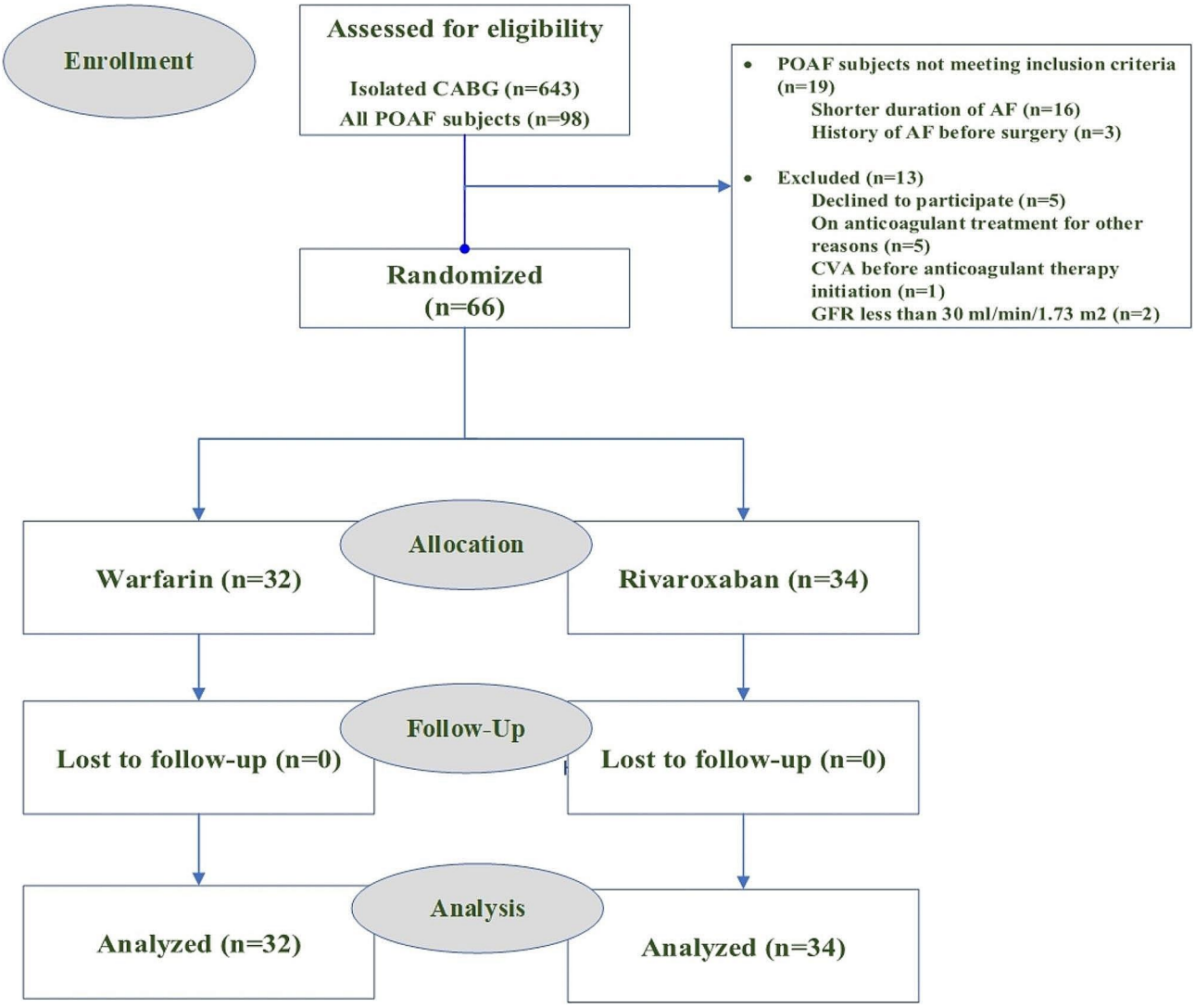

Fig. 1 CONSORT diagram. AF: Atrial Fibrillation, CABG: Coronary Artery Bypass Grafting, CVA: Cerebrovascular accident, GFR: Glomerular filtration rate, POAF: Post Operation Atrial Fibrillation

One interesting finding we came across was the apparent elevated left atrial (LA) diameter in patients who developed arrhythmia, both upon discharge and 1 month following discharge. There were significant differences in the LA size among those with AF and those with normal sinus rhythm (*P* value = 0.012 and 0.002 at discharge time and 1-month follow-up, respectively). Also, we did not discover a significant association between the number of episodes of arrhythmia and LA diameter. The comparison of LA diameter in patients with and without arrhythmia is summarized in Table 4.

Discussion

POAF as a common phenomenon following CABG surgery is believed to increase stroke incidence [22–24]. According to European Society of Cardiology guidelines, long-term oral anticoagulation therapy is a reasonable treatment strategy for preventing stroke after POAF following cardiac surgery (Class of Recommendation IIb, Level of Evidence B) [8]. Additionally, the American Heart Association/American College of Cardiology guidelines recommend anticoagulation for POAF patients (Class of Recommendation IIa, Level of Evidence B) [9]. However, the risk of bleeding events has so far stunted this application from becoming the standard approach and the overall benefit or harm of oral anticoagulation following POAF remains uncertain [2, 25].

Our study examined the risk of bleeding in POAF patients after CABG surgery, following Warfarin or Rivaroxaban administration. Our main finding, the occurrence of bleeding events, was not statistically different between the 2 groups, and overall, it was only reported in 6% of the sample. This low prevalence has also been reported by similar studies examining the effects of

Table 1 Characteristics of the patients based on their treatment

		Warfarin ($n=32$)	Rivaroxaban ($n=34$)	Total	*P* value*
Sex	Male	23 (71.9)	23 (67.6)	46 (69.7)	0.792
	Female	9 (28.1)	11 (32.4)	20 (30.3)	
Age (year)	Mean (SD)	70.59 (6.18)	66 (6.18)	68.23 (6.56)	0.005
	Median [Min, Max]	71.5 [56.0, 80.0]	65.0 [51.0, 76.0]	68.5 [51.0, 80.0]	
Weight (kg)	Mean (SD)	73.63 (11.19)	78.32 (12.61)	76.05 (12.09)	0.188
	Median [Min, Max]	73.0 [51.0, 105]	75.0 [60.0, 115]	74.0 [51.0, 115]	
Glomerular Filtration Rate (ml/min/1.73 m^2)	Mean (SD)	78.37 (17.51)	86.15 (23.39)	82.38 (20.97)	0.408
	Median [Min, Max]	80.2 [32.1, 112]	82.6 [49.0, 147]	82.0 [32.1, 147]	
Ejection Fraction (%)	Mean (SD)	43.72 (10.80)	45.44 (9.64)	44.61 (10.18)	0.582
	Median [Min, Max]	45.0 [15.0, 55.0]	50.0 [20.0, 55.0]	47.5 [15.0, 55.0]	
Left Atrial Diameter (mm)	Mean (SD)	38.59 (2.80)	38.12 (3.32)	38.35 (3.07)	0.651
	Median [Min, Max]	38.0 [34.0, 47.0]	38.0 [30.0, 46.0]	38.0 [30.0, 47.0]	
Hypertensive patients	Number (%)	21 (65.6)	31 (91.2)	52 (78.8)	0.016
Diabetic patients	Number (%)	8 [25]	12 (35.3)	20 (30.3)	0.428
Patients with Dyslipidemia	Number (%)	9 (28.1)	18 (52.9)	27 (40.9)	0.050
Smoker patients	Number (%)	7 (21.9)	6 (17.6)	13 (19.7)	0.762
Antiplatelet therapy	Aspirin	22 (68.8)	7 (20.6)	29 (44)	< 0.001
	Clopidogrel	8 [25]	25 (73.5)	33 (50)	
	Dual antiplatelet therapy	1 (3.1)	2 (5.9)	3 (4.5)	
	None	1 (3.1)	0	1 (1.5)	
HAS-BLED risk score (0–9)	Mean (SD)	2.91 (0.23)	3 (0.21)	2.95 (1.26)	0.756
	Median [Min, Max]	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	
CHA2DS2-VASc score (0–9)	Mean (SD)	2.91 (1.28)	3.00 (1.26)	2.95 (1.26)	0.761
	Median [Min, Max]	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	
Atrial Fibrillation type	Paroxysmal	28 (87.5%)	29 (85.3%)	57 (86.4%)	1
	Persistent	4 (12.5%)	5 (14.7%)	9 (13.6%)	

* *P* values were obtained using Fisher's exact test or Mann-Whitney U test

Table 2 Occurrence of bleeding events in each treatment arm

	Warfarin	Rivaroxaban	Total	*P* value*
Bleeding events	1	3	4	0.614
No events	31	31	62	
Total	32	34	66	

*Fisher's exact test

Table 3 Adverse events experienced in each treatment arm:

Adverse bleeding event Treatment arm	Warfarin ($n=32$)	Rivaroxaban ($n=34$)
Epistaxis	0	1
Oozing of sternal sutures	0	1
Cutaneous bleeding at the site of vein graft excision	0	1
Isolated hematoma	1	0
Intracranial hemorrhage	0	0
Gastrointestinal bleeding	0	0

Table 4 Left Atrial Diameter and Heart Rhythm:

		Number	Left Atrial Diameter	*P* value
At discharge time	Sinus rhythm	53	37.83 (0.34)	0.012*
	Atrial Fibrillation	13	40.46 (1.16)	
After one month	Sinus rhythm	57	37.89 (0.38)	0.002†
	Atrial Fibrillation	9	41.22 (1.01)	
Number of atrial fibrillation Episodes		1–18 3.92 (0.34)2	38.35 (0.38)	0.802‡

*Mann Whitney U test

†Data presented by mean (SD)

‡Kendall's Tau test

anticoagulants on POAF patients [26], although other studies have found this ratio to be even lower [27, 28]. This discrepancy can be attributed to our lower sample size. The insignificant difference between bleeding events for Warfarin and Rivaroxaban (*P* value=0.614) in our study, although in a smaller sample than the studies by Nauffal et al., or Patel et al., is nevertheless in agreement with their findings that bleeding events rates are similar between Warfarin and DOACs [27, 29].

The variability in bleeding rates among DOACs has been studied, revealing Rivaroxaban to exhibit the lowest safety profile [30]. In this study, we chose Rivaroxaban among other DOACs (e.g. Apixaban) as the intervention due to several reasons. Firstly, Rivaroxaban

is administered as a single dose, making it simpler for patients compared to Apixaban, which requires twice-daily dosing. This may improve patient compliance with medication regimens.

Secondly, considering the challenges of drug availability and high costs in Iran, providing Rivaroxaban was more feasible within our research budget compared to Apixaban. This decision was made to ensure that the study intervention could be implemented effectively and efficiently within the resources available.

Overall, the selection of Rivaroxaban over other DOACs in this study was based on considerations of dosing convenience for patients and cost-effectiveness within the study context.

Our study detected comparable bleeding rates between Rivaroxaban and Warfarin. Nevertheless, additional research is imperative to corroborate these observations.

In this study, none of the patients experienced thromboembolic events, and this finding is congruent with a study by Butt et al., who found anticoagulant therapy reduces the risk of thromboembolic events in POAF patients [31]. Other studies on the effects of anticoagulants on POAF have also found similar results [26–28]. While we could not compare the protective effects of Rivaroxaban and Warfarin on thromboembolic events with each other due to the fortunate lack of events in either treatment arm, similar studies have found that Rivaroxaban is either more effective at reducing the incidence of CVAs [32] or similarly effective at CVA prevention [5].

While our study found no difference in the bleeding rates of Rivaroxaban and Warfarin, a study comparing these two in non-valvular atrial fibrillation patients found that patients receiving Rivaroxaban incur less bleeding [5]. Although our study does not fully corroborate this finding, the use of Rivaroxaban over Warfarin should still be favored, since Warfarin's therapeutic effects may be altered by the use of over-the-counter medications, vitamin K deficiency, a narrow therapeutic index, and a constant need for routine INR monitoring. Rivaroxaban on the other hand is administered orally, does not have as many drug interactions, and isn't dependent on food intake. It's also important to note that among the few bleeding events we observed, they were all being administered at least one form of antiplatelet therapy along with either of the anticoagulants.

On a final note, the apparent LA enlargement in those who suffered atrial fibrillation in comparison to those who experienced normal sinus rhythms is as stated by existing literature, further highlighting the correlation between LA diameter and atrial fibrillation [33, 34]. We plan to follow up on this association in our future prospective studies to see the extent of this association and its predictive ability regarding atrial fibrillation.

Strengths and limitations

One of the strengths of our study is that, unlike most prior research, our study was a prospective and randomized design. Prospective trials in this are lacking, due to the physicians' reluctance regarding the difficult maintenance of Warfarin; however, because of the importance of this comparison of novel anticoagulants, we decided to perform a randomized trial to improve the existing literature foundation in decision-making, rather than choosing the medications based on convenience. Also, we observed no protocol violations, and our intent-to-treat analysis is the same as the per-treatment analysis.

One limitation of our study is that CABG surgery generally has the lowest risk of postoperative bleeding in comparison to other cardiac surgeries [35], therefore this work lacks generalizability to all cardiac surgeries, and further studies are warranted to compare anticoagulant-related bleeding events in other cardiac surgeries. Also, since our study lacks a placebo control group and most of the observed bleeding events were minor, we cannot state whether or not bleeding events are more common in those who take Warfarin or Rivaroxaban, in comparison to those who do not take any anticoagulants, yet it would be reasonable to assume a higher incidence among those taking any anticoagulants since a much larger study has found it to be almost 3 times more likely [27], although the risk of bleeding remains relatively low.

The lack of blinding introduces a potential source of bias in the study, as the awareness of treatment assignment could influence subjective outcomes, such as patient-reported symptoms or healthcare provider assessments. To mitigate the impact of unblinding on the study results, efforts were made to standardize outcome assessments and data collection procedures across treatment groups. Additionally, statistical analyses were conducted by researchers blinded to treatment allocation to minimize the influence of bias on data interpretation and conclusions.

While blinding is a fundamental methodological principle in clinical research to reduce bias and enhance the validity of study findings, the unique nature of the interventions in this study necessitated a pragmatic approach that prioritized patient safety and optimal clinical care.

The small sample size can be considered a limitation due to the reduced statistical power and potential difficulty in generalizing the findings to a larger population.

We performed echocardiography on all patients before surgery. However, due to some patients requiring emergency surgery and limited time, LA volume index measurement which is a more accurate method was not conducted on all patients. The parameter that was assessable in all patients in this regard was LA diameter in the parasternal long-axis view. This issue can be considered as a limitation.

Conclusions

Warfarin and Rivaroxaban are both safe and effective drugs for preventing thrombotic episodes in POAF patients who have undergone CABG surgery. The two drugs were not significantly different in terms of adverse reactions such as bleeding episodes, further supporting the tendency towards DOACs because of their convenience, less demanding maintenance, and fewer interactions.

Abbreviations

AF	Atrial fibrillation
CVA	Cerebrovascular accident
CABG	Coronary artery bypass grafting
DOACs	Direct oral anticoagulants
GFR	Glomerular filtration rate
INR	International Normalized Ratio
LA	Left Atrial
POAF	Postoperative atrial fibrillation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-024-04064-x.

Supplementary Material 1

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Author contributions

M.G., K.H and S.S. designed the study. M.G. and K.H. implemented the study. M.G., Sh.R.FA., D.A. and I.M. wrote the manuscript. M.G. revised the manuscript. A.A. performed the statistical analysis and P.P. prepared the tables.

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Nothing to declare.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to Tehran Heart Center's policy but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from each patient before recruitment and the study protocol was reviewed and approved by the ethical committees of the Tehran University of Medical Sciences with the code of: "IR.TUMS.MEDICINE.REC.1398.836". The trial was also registered in IRCT with code "IRCT20200304046696N1".

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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