Rivaroxaban versus warfarin in postoperative atrial fibrillation: Cost-effectiveness analysis in a single-center, randomized, and prospective trial

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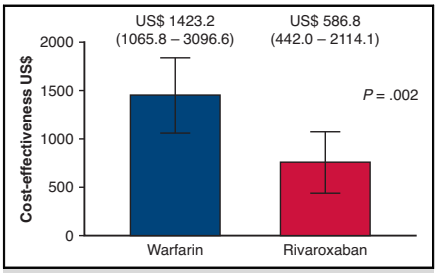
ABSTRACT

Objectives: Postoperative atrial fibrillation is the most common clinical complication after coronary artery bypass graft surgery. It is associated with a high risk of both stroke and death and increases the length of hospital stay and costs. This study aimed to evaluate anticoagulants in postoperative atrial fibrillation.

Methods: A single-center, randomized, prospective, and open-label study. The trial was conducted in Heart Institute at University of São Paulo, Brazil. Patients who developed postoperative atrial fibrillation were randomized to anticoagulation with rivaroxaban or warfarin plus enoxaparin bridging. The primary objective was the cost-effectiveness evaluated by quality-adjusted life years, using the SF-6D questionnaire. The secondary end point was the combination of death, stroke, myocardial infarction, thromboembolic events, infections, bleeding, readmissions, and surgical reinterventions. The safety end point was any bleeding using the International Society on Thrombosis and Haemostasis score. Follow-up period was 30 days after hospital discharge.

Results: We analyzed 324 patients and 53 patients were randomized. The median cost-effectiveness was $1423.20 in the warfarin group versus $586.80 in the rivaroxaban group ($P = .002$). The median cost was lower in the rivaroxaban group, $450.20 versus $947.30 ($P < .001$). The secondary outcome was similar in both groups, 44.4% in warfarin group versus 38.5% in the rivaroxaban group ($P = .65$). Bleeding occured in 25.9% in the warfarin group versus 11.5% in the rivaroxaban group ($P = .18$).

Conclusions: Rivaroxaban was more cost-effective when compared with warfarin associated with enoxaparin bridging in postoperative atrial fibrillation after isolated coronary artery bypass grafting. (JTCVS Open 2023;15:199-210)



Cost-effectiveness comparison between warfarin and rivaroxaban in POAF after isolated CABG.

CENTRAL MESSAGE

Rivaroxaban is more cost-effective than warfarin in POAF after isolated CABG, including a 52% cost reduction. Larger studies are necessary to assess hard outcomes and safety of DOACs in this scenario.

PERSPECTIVE

The presence of POAF is recognized as an independent risk for stroke, death, and increases hospital costs. No randomized studies have evaluated anticoagulation in POAF after CABG. This randomized trial show cost savings with the use of DOACs compared with warfarin, with low major bleeding rates. Our study suggests that DOACs could be an option of anticoagulation strategy in POAF after isolated CABG.

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Abbreviations and Acronyms

ACS = acute coronary syndrome
AF = atrial fibrillation/atrial flutter
AMI = acute myocardial infarction
CABG = coronary artery bypass graft
CCS = chronic coronary syndrome
DOACs = direct oral anticoagulants
GFR = glomerular filtration rate
INR = international normalized ratio
ISTH = International Society on Thrombosis and Haemostasis
LOS = length of stay
POAF = postoperative atrial fibrillation/flutter
QALY = quality-adjusted life-years

Atrial fibrillation/atrial flutter (AF) is the most common clinical complication among patients undergoing coronary artery bypass graft (CABG), occurring in almost one-third of patients.[1-3] Postoperative new atrial fibrillation/flutter (POAF) is defined as AF lasting longer than 30 seconds. POAF is classified as clinically significant when it requires anticoagulation, drug intervention to control rhythm and/or heart rate, or when it increases the length of hospital stay.[4] The peak incidence occurs between the second and fourth postoperative day with episodes of recurrence throughout hospitalization and after hospital discharge.[5]

The importance of reducing the incidence of POAF is due to the high risks associated and/or related to this arrhythmia. The presence of POAF is recognized as an independent risk for stroke, death, and also leads to an increase in length of stay (LOS) and hospitalization costs.[6-11]

Despite extensive evidence in patients with AF, few data exist on the use of anticoagulants in the setting of POAF, particularly in relation to direct oral anticoagulants (DOACs). A retrospective registry demonstrated that patients discharged with warfarin had lower rates of events, including mortality, when compared with patients not receiving anticoagulation.[10] Recent retrospective studies demonstrated DOACs as a possible option in this scenario.[12-15] One trial that compared DOACs versus warfarin in patients with POAF showed no difference in terms of bleeding outcome, and a reduction in costs close to 50% when using DOACs therapy.[12]

Thus, despite POAF being a frequent entity in clinical practice and known to be associated with a worse prognosis, it persists as an undertreated entity concerning anticoagulant therapy. The most prescribed therapy so far and considered standard in this scenario is warfarin, even in more contemporary studies, because no randomized trials have tested the use of DOACs in this scenario, raising doubts about the possible benefits of this strategy.

METHODS

Trial Design

This is a randomized, single-center, prospective, and open-label study. The study was approved by the Heart Institute of Hospital das Clinicas, University of Sao Paulo, Brazil. The ethic/research committee protocol number is SDC 5074/20/103, approval date of November 25, 2020. All patients signed an informed consent form for the publication of their study data. This study is registered at ClinicalTrials.gov (NCT05300555).

Patients and Interventions

Patients selected and randomized were those who underwent isolated CABG and developed POAF.

Inclusion Criteria

Patients with CHA_2DS_2-VASc score $\geq$2 in men and $\geq$3 in women and individuals older than age 18 years who developed 1 of these:

- POAF lasting more than 12 hours independent if needed intervention,
- POAF lasting longer than 30 seconds that requires intervention, or
- Two or more paroxysmal POAF episodes.

Exclusion Criteria

Patients were excluded if they shown an inability to sign the informed consent form, had a contraindication to DOACs anticoagulant therapy (mechanical prosthetic valve, significant mitral stenosis, or previous major bleeding that contraindicates the use of anticoagulants by clinical judgment), patients with prior AF, patients with renal dysfunction with glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 or on dialysis therapy, a pregnancy in progress, or concomitant valve surgery.

Anticoagulation

After eligibility considering the inclusion and exclusion criteria, patients were selected and randomized into 2 therapeutic groups. After randomization, anticoagulant medication was started within 24 hours.

In group 1, patients received anticoagulation with warfarin and the international normalized ratio (INR) target was between 2.0 and 3.0, associated with anticoagulation bridging with enoxaparin at a dose of 1 mg/kg every 12 hours. The warfarin prescription protocol started with 5 mg/day and if the therapeutic INR target was not achieved after 4 doses of medication, it was suggested to the clinical team to increase the dose to 7.5 or 10 mg/day depending on the patient's weight and INR of the day.

In group 2, patients received anticoagulation with rivaroxaban. The dose of rivaroxaban was 15 mg/day in patients with GFR between 30 and 49 mL/min/1.73 m^2 and 20 mg/day in patients with GFR $\geq$50 mL/min/1.73 m^2.

Randomization and, consequently, anticoagulation were performed when the patient was no longer considered at high risk of surgery-related bleeding, after being discharged from the intensive care unit, and after the removal of surgical drains. The duration of anticoagulant treatment was 30 days after hospital discharge.

Antiplatelet

After randomization, aspirin was withheld. Regarding the P2Y12 inhibitor, the protocol was: For patients who experienced acute coronary syndrome within <12 months of randomization or who had chronic coronary syndrome (CCS) angioplasty within <6 months, the use of

antiplatelet agent was preferably clopidogrel 75 mg/day in monotherapy. In addition, the patient used the anticoagulant medication of the group of randomization; For patients who had acute coronary syndrome for >12 months, or who had CCS with angioplasty for >6 months, or who underwent surgery in the context of CCS, antiplatelet medication was suspended, thus maintaining the anticoagulant medication of the group to which the patient was randomized. The antiplatelet prescription was made based on guidelines.[1,16]

Follow-up

In this study, the follow-up was for 30 days after hospital discharge. The patients included were regularly followed up with rigorous clinical evaluation during hospitalization and in a postoperative visit 30 days after discharge. Clinical events were considered from the date of inclusion in the study. In the case of patients whose hospitalization stay was prolonged and lasted longer than 30 days after randomization, the follow-up ended at this time. Patients who were discharged from hospital and had new hospitalizations between discharge and the 30-day outpatient return were also followed up on hospital readmission until the date of the 30th day of randomization.

If the patient had a bleeding event or other complications related to anticoagulant therapy, medication suspension was considered based on the risk–benefit of each situation involved. If the anticoagulant was withdrawn at any time, the return of aspirin was suggested, maintaining the usual treatment for coronary artery disease.

Costs

Hospital costs were calculated according to the supplementary health costs in Brazil and converted to US dollars. All medications had calculations based on the frequency of doses used. Cost analysis compared the cumulative costs of each therapeutic strategy over patient follow-up (Table E1). The analysis of microcosting by items was also performed separately. The resources analyzed in the index hospitalization were number of days hospitalized after randomization and price of intervention medications. In the case of readmissions between hospital discharge and outpatient return, the following costs were calculated: related complications and use of resources related to readmission, complementary exams performed, and number of days in hospital.

Quality of Life Questionnaire and Cost-Effectiveness Analysis

The SF36 is a generic quality of life questionnaire, consisting of 36 questions.[17,18] The SF-6D questionnaire, derived from the SF36, has already been validated and assesses the physical and emotional domains (Figure E1). The score consists of 6 questions with multiple alternatives, with the patient selecting only 1 alternative for each question. The best score, that is, the "best quality of life" corresponds to 6 points and the worst score, that is, the "worst quality of life" corresponds to 31 points.

Figure E2 demonstrates, in a practical way, how the score obtained in the SF-6D questionnaire is equivalent to a quality-adjusted life-years (QALY), in our study. The best functional status (score 6 on the SF-6D questionnaire) is equivalent to QALY 1 and the worst functional status (score 31 on the SF-6D questionnaire) is equivalent to QALY 0.[19]

Thus, based on the analysis of the SF-6D, it becomes possible to calculate the QALYs. QALYs are obtained by the individual's survival over the analyzed time, multiplied by the quality of life, measured through specific questionnaires. Its advantage is that it provides a common unit of cost-effectiveness of different health interventions.[20,21] The SF-6D questionnaire was applied at the end of the patients' follow-up.

In cost-effectiveness analysis, costs are measured in monetary units and effectiveness in QALYs. The results are expressed by a quotient, where the numerator is cost and the denominator is effectiveness, with the result in monetary units. Cost-minimization analysis is performed when there is strong evidence of equivalent effectiveness between competing alternatives, and only when the valuation of other parameters (eg, mild adverse effects or method of use) is not expected to significantly affect the quality of life of users.

Trial End point

The primary end point was the comparison of cost-effectiveness between both anticoagulation strategies: warfarin associated with enoxaparin bridging (group 1) versus rivaroxaban (group 2) in patients who had POAF during the hospitalization period and 30-day follow-up. The SF-6D quality of life questionnaire was used to calculate the QALY. The secondary end point was considered the composite outcome of the following events: mortality, stroke, acute myocardial infarction (AMI), readmission, systemic embolization, surgical reintervention, bleeding using the International Society on Thrombosis and Haemostasis (ISTH) score, infection, and the safety outcome was the bleeding assessment according to the ISTH bleeding score and the exploratory end point was the cost-minimization analysis.

Statistical Analysis

The evaluation of the distribution of continuous variables was performed using the Kolmogorov-Smirnov test. Quantitative variables were expressed as mean $\pm$ SD or median (interquartile range). Qualitative variables were expressed as absolute and relative frequencies. Comparison of means of quantitative variables was performed using Student t test. When normality was rejected, the Mann-Whitney method was used. The evaluation of homogeneity between proportions was performed using the χ^2 test or Fisher exact test. Event rates were estimated using the Kaplan-Meier curve and differences between groups using the log-rank test and logistic regression analysis and the Cox method to establish the risk for the occurrence of events between groups. In the statistical analysis, SPSS software version 21.0 (IBM-SPSS Inc) was used.

RESULTS

Three hundred twenty-four patients who underwent CABG were evaluated. From this sample, 53 patients were included and randomized. All patients were followed-up until the end of the study and completed the SF-6D questionnaire as shown in the flowchart (Figure 1).

Baseline patient characteristics were similar between the groups (Table 1). Prior medication use was similar in both groups, except for beta-blockers. Surgery in the setting of CCS predominated. The mean CHA_2DS_2-VASc score was similar in both groups. The HAS-BLED score had a median of 1 in both groups.

The surgical techniques were similar in both groups. The peak incidence of POAF occurred between the second and third postoperative day and the median duration was 14 hours in the warfarin group and 26 hours in the rivaroxaban group ($P = .17$). Rhythm control with amiodarone predominated in the included patients.

The median prescription of anticoagulant medications started on the seventh postoperative day in the warfarin group and on the eighth day in the rivaroxaban group ($P = .83$). Median days in hospital after randomization were 5 days in the warfarin group and 2 days in the rivaroxaban group. Prescription of antiplatelet drugs concomitant with anticoagulant therapy was similar in both groups (Table 2).

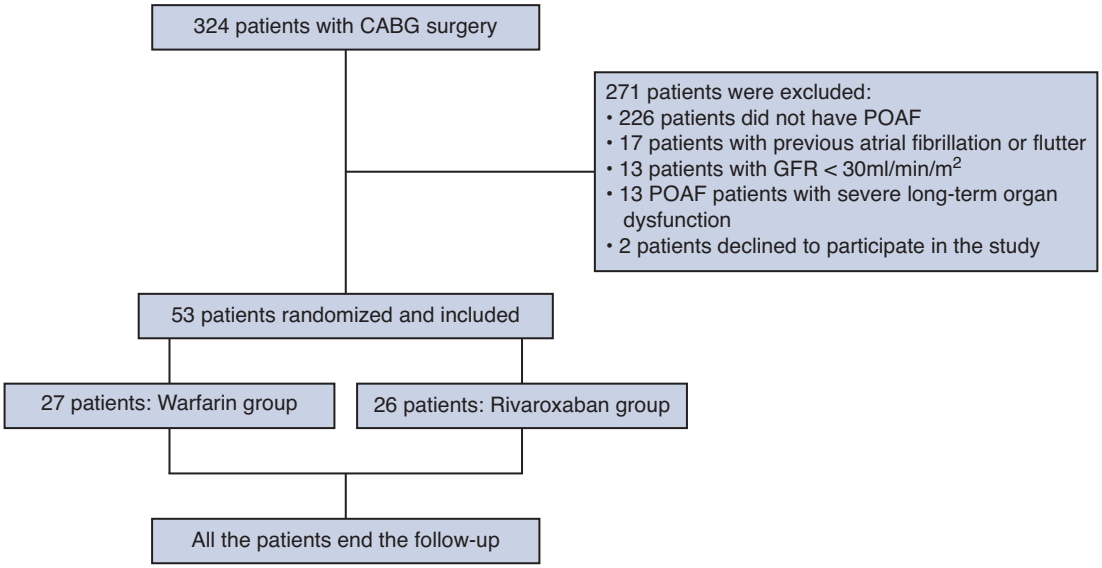

FIGURE 1. Patient selection and follow-up flow chart. *CABG*, Coronary artery bypass graft; *POAF*, postoperative atrial fibrillation; *GFR*, glomerular filtration rate.

The primary outcome demonstrated that the anticoagulation strategy with rivaroxaban was more cost-effective when compared with the warfarin group. The median for group 1 was $1423.20 and for group 2 was $586.80 ($P = .002$) (Figure 2). The cost-minimization analysis showed cost savings of $497.10 or 52.4% when using the anticoagulation strategy with rivaroxaban because the costs had a median of $947.30 in the warfarin group and $450.20 in the rivaroxaban group. The individual group costs, SF-6D quality of life questionnaire and consequent QALY were similar in both groups (Table 3).

When analyzing the micro-costing (Figure 3), it was observed that the main factors that led to higher costs in both groups were the days of the index hospitalization and the cost of the medications used. Costs related to general exams, laboratory exams, readmissions, and procedures were not very relevant when compared with the total amount and there was no statistical difference when comparing both groups (Table 3).

When comparing the costs related to medication prescription in both groups, there was a higher cost in the warfarin group, due to the bridging therapy with enoxaparin. The median LOS after randomization in the warfarin group was 5 days versus 2 days in the rivaroxaban group ($P = .01$), which led to higher costs related to hospital stay in the warfarin group.

The composite end point of death, AMI, stroke, thromboembolic events, bleeding, infection, readmissions, and surgical reintervention was similar in both groups, with a rate of 44.4% in the warfarin group and 38.5% in the rivaroxaban group ($P = .65$) (Table 4). There were no deaths, AMI, stroke, or thromboembolic events in the study. The presence of any bleeding, defined by the ISTH score, was 25.9% in group 1% and 11.5% in group 2, $P = .18$. The rate of major bleeding was low in our study with only 2 patients (3.7%) in the warfarin group and none in the rivaroxaban group. (Table E2).

DISCUSSION

Our trial demonstrated that the strategy of using rivaroxaban was more cost-effective compared with warfarin with enoxaparin bridging in POAF after CABG, mainly due to the reduction in hospital costs related to this medication, given the need to reach a therapeutic target with the use of warfarin and because DOACs do not need to achieve therapeutic level. The median length of stay was 5 days in the warfarin group versus 2 days in the rivaroxaban group and those 3 more days in the warfarin group significantly raised the hospital costs. In the microcosting analysis, both the hospital LOS and the use of enoxaparin led to higher costs in the warfarin group. The use of bridging with enoxaparin was done following guidelines recommendations.[22,23] Moreover, the use of DOACs led to a 52.4% reduction in costs. In our study, there were no cardiovascular events and the presence of bleeding was similar in both groups (Figure 4).

The presence of POAF is recognized as an independent risk for stroke and death. A previous multicenter registry with more than 16,000 patients who underwent CABG showed a 21% increase in mortality in the POAF group, in the follow-up of 6 years, when compared with the group that did not present such arrhythmia.[10] In meta-analyses published in 2015 and 2019, including more than 2 million patients, POAF was associated with a higher risk of stroke and mortality in the 30-day and long-term follow-up of these patients.[7,8] There is also an increased incidence of

TABLE 1. Comorbidities, use of medication, and relevant tests before patient randomization

	Warfarin (n = 27)	Rivaroxaban (n = 26)	*P* value
Baseline			
Sex (%)	Male = 85.2	Male = 61.5	.051
	Female = 14.8	Female = 38.5	
Age (y)	67 ± 7	65 ± 7	.85
Hypertension (%)	92.6	92.3	.96
Diabetes (%)	44.4	65.4	.12
Dyslipidemia (%)	100	100	1.0
Peripheral arterial disease (%)	3.7	7.7	.53
Chronic obstructive pulmonary disease (%)	0	0	1.0
Previous stroke (%)	14.8	7.7	.41
Smoker (%)	33.3	23.1	.40
Glomerular filtrate rate (mL/min/m^2)	68.8 ± 24.2	70.5 ± 28	.81
CHA_2DS_2-VASc	3.85 ± 1.35	3.88 ± 1.45	.96
HAS-BLED	1 (1-2)	1 (1-1)	.02
Echocardiogram			
Atrium size (mm)	42 ± 7	42 ± 7	.95
Atrium volume (mL/m^2)	38 ± 9	40 ± 12	.68
Ejection fraction (%)	53 ± 12	58 ± 10	.10
Previous medication (%)			
SGLT2 inhibitors (%)	3.7	3.8	.97
GLP1 agonist (%)	0	0	1.0
Insulin (%)	7.4	38.5	.07
Metformin (%)	44.4	65.4	.12
Amiodarone (%)	0	3.8	.30
Beta-blocker (%)	85.2	57.7	.02
P2Y12 inhibitor (%)	29.6	38.5	.49
Aspirin (%)	100	100	1.0
Diuretic (%)	14.8	34.6	.09
Estatin (%)	100	100	1.0
ACE inhibitor (%)	74.1	76.9	.81
CAD context			
CCS (%)	66.7	65.5	.62
Non-ST ACS (%)	14.8	23.0	
STEMI (%)	18.5	11.5	
Surgery (%)			
ECC (%)	85.2	80.8	.66
ECC time (min)	98 ± 28	99 ± 21	.89
ACCT (min)	82 ± 26	87 ± 21	.51
Arterial graft (%)	0-0	0-3.8	.34
	1-100	1-92.3	
	2-0	2-3.8	
Venous graft (%)	0-18.5	0-19.2	.57
	1-18.5	1-30.8	
	2-59.3	2-50.0	
	3-3.7	3-0	
POAF data			
Duration of POAF (h)	14 (4-44)	26 (9-72)	.17
Days of incidence of POAF	3.41 ± 2.0	2.62 ± 0.85	.17
Amiodarone in POAF (%)	100	100	1.0

Values are presented as %, mean ± SD, or range, unless otherwise noted. *SGLT2*, Sodium glucose linked transporter; *GLP1*, glucagon-like peptide-1; *ACE*, angiotensin-converting enzyme; *CAD*, coronary artery disease; *CCS*, chronic coronary syndrome; *Non-ST ACS*, non-ST elevation acute coronary syndrome; *STEMI*, ST-segment elevation myocardial infarction; *EEC*, extracorporeal circulation; *ACCT*, aortic crossclamp time; *POAF*, postoperative atrial fibrillation.

TABLE 2. Data regarding anticoagulation prescription

	Warfarin (n = 27)	Rivaroxaban (n = 26)	*P* value
Anticoagulant prescription			
Anticoagulant initiation day after surgery	7 (6-8)	8 (7-8)	.83
Days hospitalized after randomization	5 (4-7)	2 (1-5)	.01
Wafarin doses up to target INR	5.42 ± 3.59		
Enoxaparin doses during hospitalization	9.81 ± 6.02		
Rivaroxaban doses during hospitalization		3.54 ± 2.48	
No. of INR performed after hospital discharge	2.2 ± 0.93		
INR in therapeutic goal after hospital discharge (%)	55.2 ± 29.5		
Antiplatets prescription (%)	44.5	30.8	.30

Values are presented as mean ± SD unless otherwise noted. *INR*, International normalized ratio.

hospitalization for heart failure, in patients with no previous history of heart failure, who developed POAF.[24] In the subanalysis of EXCEL trial, patients who had new AF in the surgical group had a major independent risk factor for death and stroke at the 3-year follow-up.[25]

Moreover, POAF increases LOS and costs. Lapar and colleagues[11] evaluated more than 49.000 patients who underwent cardiac surgery and 19% developed AF. In patients undergoing CABG, POAF was associated with ICU LOS >47 hours, ICU costs >$2700, and total hospitalization costs greater than $7600.[11] Estimates of the average annual cost of treatment of POAF and its sequelae approach $1 billion in the United States.[26]

A previous study[3] demonstrated that patients who had POAF were discharged in sinus rhythm, regardless of the strategy of rhythm or rate control used in POAF. Ahlsson and colleagues[27] demonstrated that in 5 years, AF recurrence was more present in patients who developed POAF (25.5% vs 3.5%) when compared with those who did not develop this arrhythmia. Meta-analysis results point out an incidence of 28.3% of AF among patients who were monitored using noninvasive techniques during 2 to 4 weeks after hospital discharge. In patients who had implanted devices with continuous monitoring for arrhythmia assessment, AF was detected in 60% to 100% of the patients, and many of them were asymptomatic.[28]

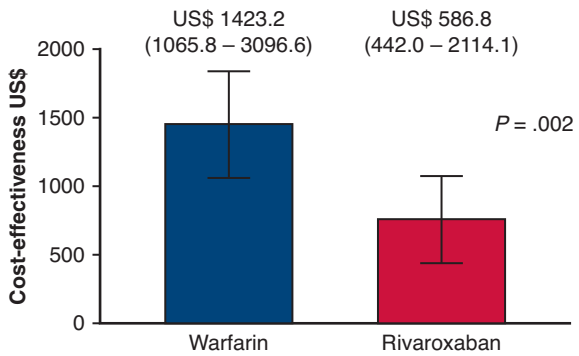

FIGURE 2. Cost-effectiveness analysis.

Thus, it is evident that although many patients return to sinus rhythm during hospitalization and at hospital discharge, the presence of paroxysmal AF is common and increases the risk of thromboembolic and cardiovascular events for these patients over time. Despite the importance of POAF, the most effective management strategy for this common surgical complication remains uncertain, a factor that had led to a substantial variation in treatments, including in the use of anticoagulant therapy. The current guidelines[22,23] recommended that patients should be discharged from the hospital with anticoagulation prescription for at least 4 weeks and the CHA_2DS_2-VASc score should be considered, as well as the risk of bleeding. The use of anticoagulation therapy should be started during hospitalization and the bridge with enoxaparin or unfractionated heparin is recommended. Despite current recommendations, the use of anticoagulants in this scenario is still rare. Some studies[10,18] have published that the anticoagulation prescription rate is low (10%-25%) and predominantly with warfarin, even in more recent publications when DOACs were already widely used in other scenario. Naik and

TABLE 3. Data referring to the microcosting, SF-6D, and quality-adjusted life years (QALY) of both groups

	Warfarin (n = 27)	Rivaroxaban (n = 26)	*P* value
QALY	0.7 ± 0.21	0.62 ± 0.24	.22
SF-6D questionnaire	12 (10-15)	14 (11-18)	.23
Total costs ($)	947.3 (699.3-1644.9)	450.2 (347.4-752.1)	<.001
Medications ($)	168.3 (131.8-257.9)	44.2 (42.9-45.6)	<.001
Hospitalization ($)	710.5 (609.0-1015.0)	406.0 (304.5-710.5)	.002
Readmission ($)	184.2 ± 473.6	15.6 ± 79.6	.15
General exams ($)	73.6 ± 231.6	8.5 ± 78.4	.16
Laboratorial exams ($)	21.3 ± 54.9	0.3 ± 1.8	.15
VAC therapy ($)	7.8 ± 28.1	0	.16
Other costs ($)	56.7 ± 294.2	2.1 ± 11.1	1.0

Values are presented as median (range) or mean ± SD unless otherwise noted. *QALY*, Quality-adjusted life years; *VAC*, vacuum-assisted closure.

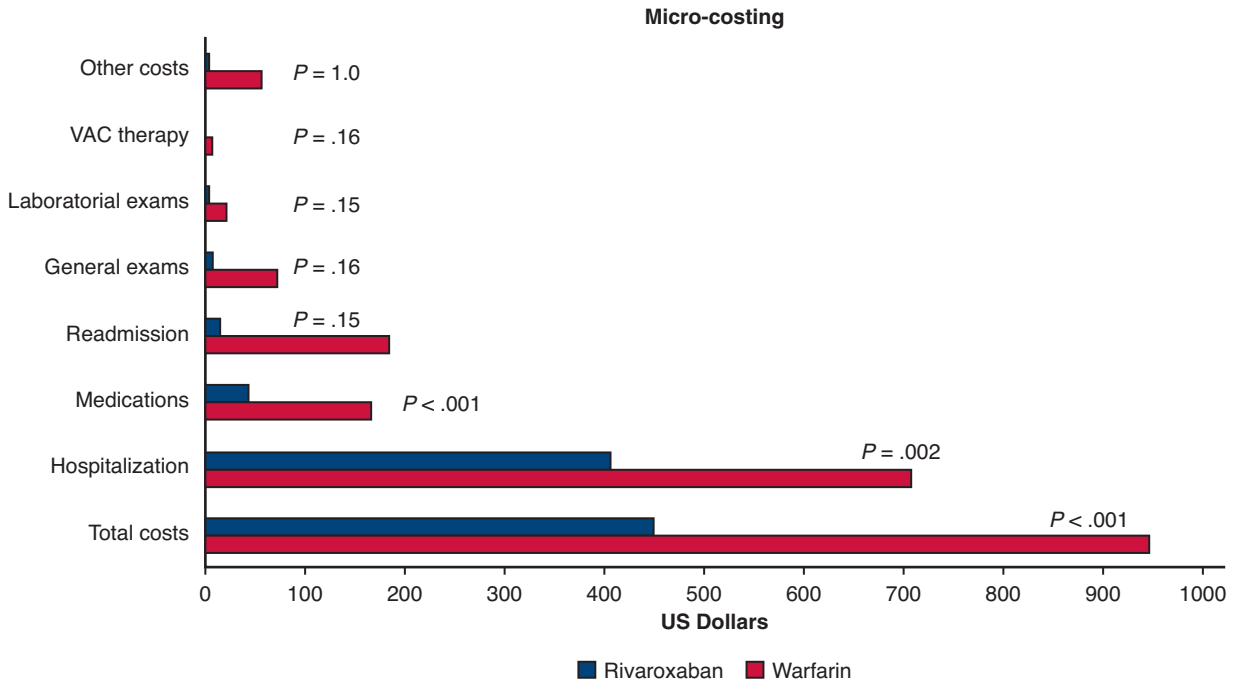

FIGURE 3. Micro-costing analysis. *VAC*, Vacuum-assisted closure.

colleagues[14] compared warfarin versus DOAC in 194 patients within 7 days after cardiac surgery, with low major bleeding rates (4.1% vs 2.1%) and no difference in groups. Another study evaluated DOACs retrospectively after cardiac surgery, and report few major and minor bleeding in this population, although 3 patients (17%) with rivaroxaban had major bleeding.[15] Major bleeding of those studies is similar with our trial.

By having a predictable effect, not requiring control with laboratory tests or bridging therapy, the use of DOACs becomes attractive in the most diverse clinical scenarios. Specifically in the postoperative period, this type of therapy could reduce the hospital LOS, given that there is no need to adjust the dose to reach the therapeutic target because the prothrombin time test is necessary in patients receiving anticoagulation with warfarin. Some antidotes to reduce bleeding associated with anti-XA therapy have been described and present a possible option when bleeding occurs while using DOACs.[29,30] Those therapies could be more effective than multiples transfusions that are necessary when bleeding occurs with warfarin and if further reoperations are needed, those antidotes could correct the clotting factors earlier. Despite this, very little research is dedicated to exploring this class of drugs in the postoperative course of CAGB.

TABLE 4. Secondary end point

	Warfarin (n = 27)	Rivaroxaban (n = 26)	*P* value
Secondary end point	12 (44.4)	10 (38.5)	.65
Death	0	0	1.0
ACS	0	0	1.0
Stroke	0	0	1.0
Thromboembolic events	0	0	1.0
Infection	8 (29.6)	6 (23.1)	.58
Any bleeding	7 (25.9)	3 (11.5)	.18
Readmission	3 (11.1)	1 (3.8)	.31
Reoperation	1 (3.7)	0	.32

Values are presented as n (%) unless otherwise noted. *ACS*, Acute coronary syndrome.

The study has some limitations. First, the primary outcome was the short-term cost-effectiveness assessment. Previous publications have evaluated the cost-effectiveness using QALY over a long-term period. However, our study was a pioneer in a short-term evaluation and the cost-minimization analysis demonstrated lower costs associated with DOAC and the SF-6D questionnaire were similar between the groups. Second, the study lacks the power to assess the hard outcome, including bleeding, given the small included population. Thus, larger studies are needed to assess hard outcomes when comparing anticoagulation strategies and to compare anticoagulation versus non-anticoagulation in these patients in the short- and long-term scenarios. Third, costs were calculated in Brazilian Real R$ and converted into US dollars, leading to apparently low costs. However, the main idea of reducing costs by more than 50% remains. Fourthly, because the study was carried

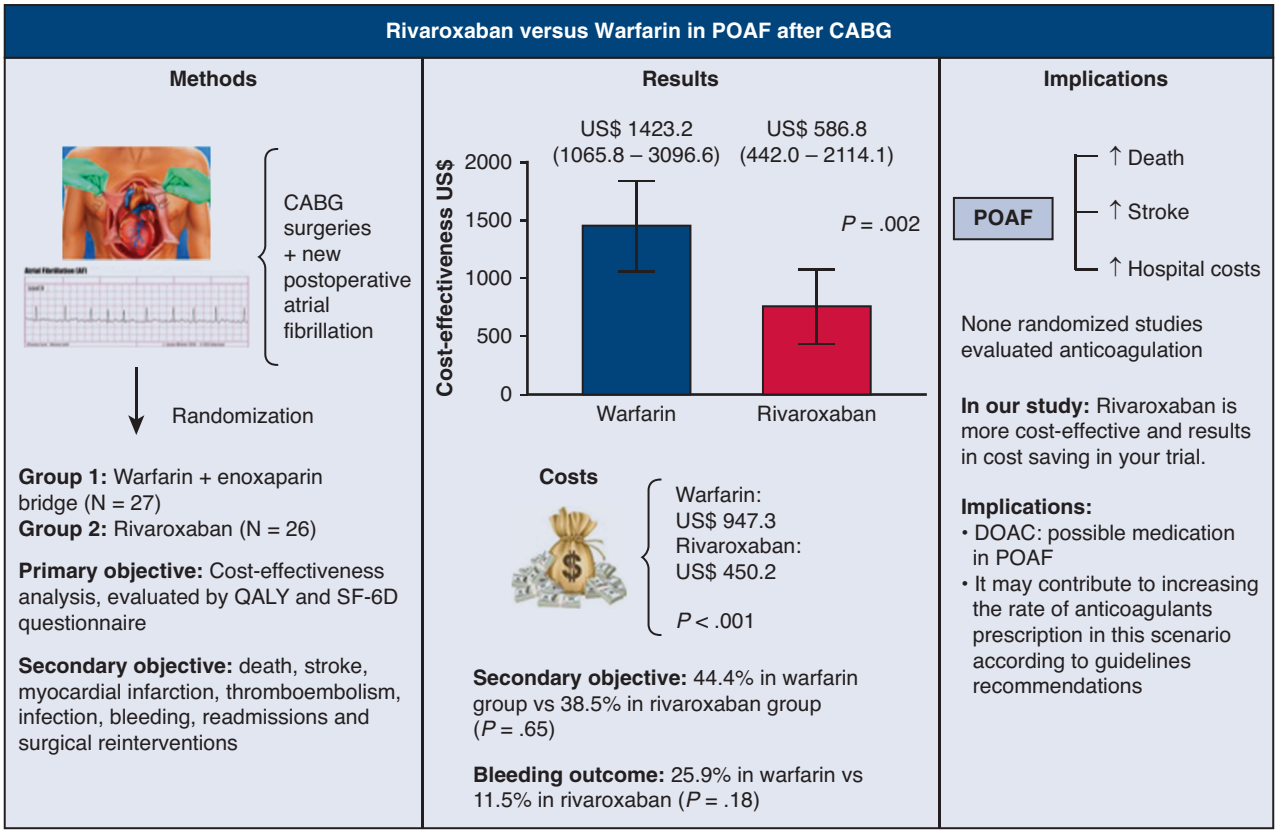

FIGURE 4. The presence of POAF is recognized as an independent risk for stroke, death, and increased hospital costs. No previous randomized studies evaluated anticoagulation in POAF after CABG. This randomized trial shows cost savings with the use of DOAC compared with warfarin, with low major bleeding rates. Our study suggests that DOAC could be an option of anticoagulation strategy in POAF after isolated CABG. *POAF*, Postoperative atrial fibrillation; *CABG*, coronary artery bypass graft; *QALY*, quality-adjusted life years; *DOAC*, direct oral anticoagulant.

out during the global COVID-19 pandemic, fewer surgeries were performed, and more difficulty was found in patient inclusion and long-term follow-up. Fifthly, our trial evaluated only patients after isolated CABG. Thus, our results could not be extrapolated to other cardiac procedures such as valve surgeries.

Finally, this is the first randomized study that evaluated the comparison of anticoagulation in POAF, including DOACs therapy. Thus, our trial is a pilot study that suggests that DOAC is a possible option when compared with warfarin associated with enoxaparin bridging, and that this strategy reduces the costs and LOS of these patients, with less burden on the health system.

Furthermore, the use of anticoagulants is low in this setting and no randomized studies already have yet tested the DOACs strategy in POAF after isolated CABG. Larger, multicenter studies are needed to assess hard outcomes, to assess if DOACs are a safe option after CABG, and to assess other cardiac surgeries such as valve replacement.

CONCLUSION

In our sample of patients with POAF after isolated CABG, anticoagulation with rivaroxaban was more cost-effective when compared with warfarin.

IMPLICATION STATEMENT

The presence of POAF is recognized as an independent risk for stroke, death, and increased hospital costs. No previous randomized studies evaluated anticoagulation in POAF after CABG. This randomized trial shows cost savings with the use of DOAC compared with warfarin, with low major bleeding rates. Our study suggests that DOAC could be an option of anticoagulation strategy in POAF after isolated CABG.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or

reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: postoperative atrial fibrillation, anticoagulation, direct oral anticoagulant, coronary artery bypass surgery, cost-effective, costs

Physical functioning
1. Your health does not limit you in vigorous activities
2. Your health limits you a little in vigorous activities
3. Your health limits you a little in moderate activities
4. Your health limits you a lot in moderate activities
5. Your health limits you a little in bathing and dressing
6. Your health limits you a lot in bathing and dressing

Role limitation
1. You have no problems with your work or other regular daily activities as a result of your physical health or any emotional problems
2. You are limited in the kind of work or other activities as a result of your physical health
3. You accomplish less than you would like as a result of emotional problems
4. You are limited in the kind of work or other activities as a result of your physical health and accomplish less than you would like as a result of emotional problems

Social functioning
1. Your health limits your social activities none of the time
2. Your health limits your social activities a little of the time
3. Your health limits your social activities some of the time
4. Your health limits your social activities most of the time
5. Your health limits your social activities all of the time

Pain
1. You have no pain
2. You have pain, but it does not interfere with your normal work (both outside the home and housework)
3. You have pain that interferes with your normal work (both outside the home and housework) a little bit
4. You have pain that interferes with your normal work (both outside the home and housework) moderately
5. You have pain that interferes with your normal work (both outside the home and housework) quite a bit
6. You have pain that interferes with your normal work (both outside the home and housework) extremely

Mental health
1. You feel tense or downhearted and low none of the time
2. You feel tense or downhearted and low a little of the time
3. You feel tense or downhearted and low some of the time
4. You feel tense or downhearted and low most of the time
5. You feel tense or downhearted and low all of the time

Vitality
1. You have a lot of energy all of the time
2. You have a lot of energy most of the time
3. You have a lot of energy some of the time
4. You have a lot of energy a little of the time
5. You have a lot of energy none of the time

FIGURE E1. SF-6D.

Points	6	7	8	9	10	11	12	13
Qaly	1	0.96	0.92	0.88	0.84	0.80	0.76	0.72

Points	14	15	16	17	18	19	20	21	22
Qaly	0.68	0.64	0.60	0.56	0.52	0.48	0.44	0.40	0.36

Points	23	24	25	26	27	28	29	30	31
Qaly	0.32	0.28	0.24	0.20	0.16	0.12	0.08	0.04	0

FIGURE E2. Equivalence between SF-6D questionnaire and quality-adjusted life years (*QALY*).

TABLE E1. Costs according to supplementary health in Brazil and converted to US dollars

Item	US$
Daily hospitalization	101.50
Medications	
Enoxaparin (dose)	20.90
Rivaroxaban (dose)	1.34
Warfarin (dose)	0.18
Laboratory tests per day (readmission)	11.78
Imaging exams (readmission)	
Computed tomography scan with contrast	339.00
Computed tomography scan	221.00
Chest ultrassound	12.93
Adbomen ultrassound	32.08
Echocardiogram	55.87
Procedures	
Vacuum-assisted closure	35.14
Thoracentesis	57.01
Red blood cell transfusion	185.49
Fresh frozen plasma transfusion	209.48

TABLE E2. Bleeding rates classification

	Warfarin (N = 27)	Rivaroxaban (N = 26)	*P* value
ISTH classification			.36
	0 = 74.1%	0 = 88.5%	
	1 = 3.7%	1 = 7.7%	
	2 = 14.8%	2 = 3.8%	
	3 = 3.7%	3 = 0%	
	4 = 3.7%	4 = 0%	

ISTH, International Society on Thrombosis and Haemostasis.