American Journal of Cardiovascular Drugs
https://doi.org/10.1007/s40256-020-00449-3

ORIGINAL RESEARCH ARTICLE

Rivaroxaban Versus Warfarin in Patients with Mechanical Heart Valves: Open-Label, Proof-of-Concept trial—The RIWA study

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Accepted: 22 October 2020

Abstract

Background and Purpose To date, vitamin K antagonists are the only available oral anticoagulants in patients with mechanical heart valves. In this way, we developed a pilot trial with rivaroxaban.

Methods The RIWA study was a proof-of-concept, open-label, randomized clinical trial and was designed to assess the incidence of thromboembolic and bleeding events of the rivaroxaban-based strategy (15 mg twice daily) in comparison to dose-adjusted warfarin. Patients were randomly assigned in a 1:1 ratio and were followed prospectively for 90 days.

Results A total of 72 patients were enrolled in the present study. Of these, 44 patients were randomized: 23 patients were allocated to the rivaroxaban group and 21 to the warfarin group. After 90 days of follow-up, the primary outcome occurred in one patient (4.3%) in the rivaroxaban group and three patients (14.3%) in the warfarin group (risk ratio [RR] 0.27; 95% confidence interval [CI] 0.02–2.85; $P = 0.25$). Minor bleeding (without discontinuation of medical therapy) occurred in six patients (26.1%) in the rivaroxaban group versus six patients (28.6%) in the warfarin group (RR 0.88; 95% CI 0.23–3.32; $P = 0.85$). One patient in the warfarin group died from myocardial infarction. No cases of hemorrhagic stroke, valve thrombosis, peripheral embolic events, or new intracardiac thrombus were related in both groups.

Conclusions In this pilot study, rivaroxaban 15 mg twice daily had thromboembolic and bleeding events similar to warfarin in patients with mechanical heart valves. These data confirm the authors' proof-of-concept and suggest that a larger trial with a similar design is not unreasonable.

ClinicalTrial.gov identifier NCT03566303.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40256-020-00449-3) contains supplementary material, which is available to authorized users.

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Key Points

There are very limited data on the use of direct oral anticoagulants in patients with mechanical heart valves (MHVs).

This is the first randomized clinical trial involving the comparison of a factor Xa inhibitor and warfarin in patients with MHVs.

This study is useful as a hypothesis generator for a large randomized study.

Published online: 05 November 2020

1 Introduction

Valvular heart disease (VHD) affects thousands of people worldwide. It is estimated that 90,000 valve prostheses are implanted in the United States and 280,000 are implanted worldwide per year [1]. Mechanical heart valves (MHVs) have great durability; however, they require lifelong anticoagulation medication. Despite the good applicability of the use of warfarin (a vitamin K inhibitor) to reduce thromboembolisms in patients with MHVs, the risk of cerebral embolism is about 3% per year [2], and its use requires intensive laboratory control, in addition to it presenting diverse drug interactions, having a long half-life, and requiring supplement restrictions [3]. Such patients, mainly with prosthesis in the mitral position, have poor international normalized ratio (INR) control, even though they are in specialized clinics [4].

Direct oral anticoagulants (DOACs) were developed as a suitable alternative to vitamin K antagonists, and several studies have evaluated the ability of DOACs to prevent thromboembolic and bleeding events in comparison to vitamin K antagonists [5]. They are associated with a lower risk of both fatal/disabling and non-disabling stroke [6], and are a reasonable alternative to warfarin in atrial fibrillation (AF) patients with VHD [7]. In addition, they offer several advantages over warfarin, including the elimination of routine laboratory monitoring, fewer drug and supplement interactions, and rapid therapeutic onset and offset.

Dabigatran (an oral direct thrombin inhibitor) was the only DOAC tested in patients with MHVs. However, it showed negative results in both efficacy and safety outcomes, leading to early interruption of the RE-ALIGN study [8]. In vitro and animal models with MHVs have shown promising results with the use of rivaroxaban, a factor Xa (FXa) inhibitor, in the prevention of thromboembolic events [9, 10]. The aim of the current study was to compare the use of rivaroxaban versus warfarin in the prevention of thromboembolic and bleeding events in MHV patients.

2 Methods

2.1 Study Design

The RIWA study (ClinicalTrials.gov NCT03566303) is a randomized, open-label, unicentric, proof-of-concept trial. The trial protocol was approved by the local ethics committee and was monitored in accordance with Good Clinical Practice (GCP) standards.

2.2 Study Population and Randomization

Trial enrollment began on July 17, 2018 and ended on March 16, 2020. Patients were eligible for inclusion if they were between the ages of 18 and 74 years and had undergone implantation of a bileaflet mechanical mitral and/or aortic valve, for which at least 3 months had passed since the operation before randomization. Participants were selected from General Hospital Roberto Santos in Salvador-Brazil. Complete exclusion criteria are provided in the Supplementary Appendix (see the electronic supplementary material). All patients provided written informed consent before enrollment. The trial rationale and design have been published previously [11].

To participate in the study, participants routinely underwent a head computed tomography (CT) scan (without contrast) and a transesophageal echocardiogram (TEE). After 90 days of follow-up, a new head CT scan and TEE were repeated in all patients. This strategy aimed to increase accuracy in the detection of thrombotic and embolic events in the heart and brain.

Patients were randomly assigned to receive rivaroxaban or warfarin in a ratio of 1:1. The randomization was performed using a random number table, generated by a computerized electronic system. Patients randomized with an "even number" were allocated to the rivaroxaban group, and patients with an "odd number" were allocated to the warfarin group, respectively. Next, each number in the random table was sequentially placed in a sealed, opaque envelope that was opened by the researcher only at the time of randomization of each recruited patient. The patient and the researcher only knew about the number drawn (and thus the selected drug) at the time of opening the envelope. Another researcher witnessed the entire consultation for surveillance of the technique performed.

2.3 Study-Drug Regimen and Follow-up

For patients in the rivaroxaban group, the dosing algorithm that we tested in all patients was 15 mg twice daily (BID). Rivaroxaban was started only when the INR was < 3.0, and all patients were instructed to ingest the tablet with food in order to optimize the absorption of the drug.

Patients assigned to warfarin require close coagulation monitoring to achieve the target INR (range 2.5–3.5 for mitral and aortic position if there is presence of AF, or range 2.0–3.0 for isolated aortic position without AF). A warfarin dose-adjustment algorithm was used according to the evidence-based guidelines [12, 13]. A modified Rosendaal method of linear interpolation was used between each pair of measured INR values [14]. For

patients with INR values outside the therapeutic range, measurements were repeated every 7 days for at least 3 months to improve time-in-therapeutic-range accuracy [15].

The use of drugs such as acetylsalicylic acid, clopidogrel, and other antiplatelet agents was not allowed during the study period. The same applied to other drugs that interact with rivaroxaban, such as combined P-gp and strong CYP3A4 inhibitors or strong CYP3A4 inducers, which increase or decrease rivaroxaban's effects, respectively.

All the patients who underwent randomization were to be followed through 90 days. During this period, they were contacted by phone every 7 days and had a face-to-face consultation every 30 days and whenever necessary for clinical reasons. Patients with possible symptoms were instructed to request immediate medical attention in the hospital's emergency department.

2.4 Study Outcomes

The primary efficacy outcome was the composite of stroke, transient ischemic attack (TIA), silent brain infarction (SBI), and systemic embolism (SE). A key secondary efficacy outcome was the composite of stroke/TIA/SBI/SE and death from any cause. Other secondary outcomes included were acute myocardial infarction (AMI), valve thrombosis, and new intracardiac thrombus.

The primary safety outcome was major or clinically relevant non-major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria and Bleeding Academic Research Consortium (BARC) scale [16, 17]. Other secondary outcomes of safety included minor bleeding. All clinical events were defined in the study protocol and were adjudicated by an independent committee whose members were unaware of the study group assignments. Complete outcome definitions are provided in the Supplementary Appendix (see the electronic supplementary material).

2.5 Statistical Analysis

The primary efficacy and safety analyses are conducted on the full analysis set of all randomized patients according to the intention-to-treat principle, using end points blindly adjudicated by an independent clinical event committee. SPSS 24.0 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical analysis of the collected data. Baseline data are reported as means and standard deviations for continuous data and as numbers and percentages for categorical data. Outcomes were analyzed with the use of time-to-event methods. Cox proportional hazards modeling was used for efficacy and safety analyses. Paired *t* test was applied for intra-group comparison when the differences of the pairs presented a normal distribution with Kolmogorov-Smirnov and Shapiro–Wilk normality tests. Otherwise, the Wilcoxon signed-rank was used. A *P* value of 0.05 or less was considered to indicate statistical significance.

3 Results

3.1 Patients and Follow-up

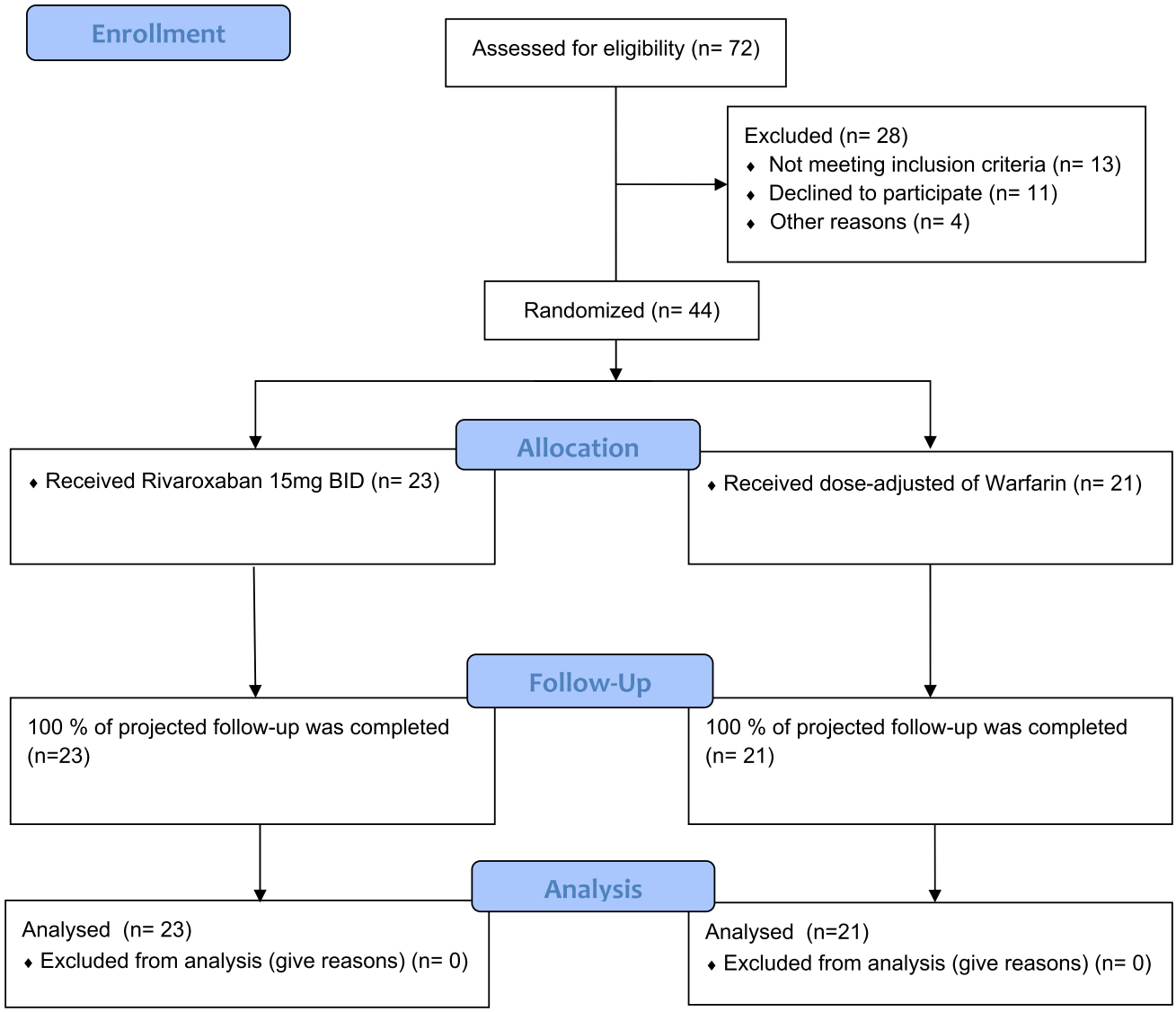
From July 17, 2018 through to March 16, 2020, we recruited 72 patients with mitral and/or aortic MHVs at least 3 months after replacement, as detailed in Fig. 1. Baseline characteristics are summarized in Table 1. The mean and median age was approximately 45 years, 61.3% of the patients were women, 36 (81.8%) had a history of rheumatic fever in childhood, 17 (38.6%) had previous AF, and the mean time between postoperative valve replacement and randomization was approximately 56.6 months. The mean CHA_2DS_2-VASc (an index of the risk of stroke in patients with AF) and HAS-BLED (an index for assessment of major bleeding risk for patients on anticoagulation) scores were 2.34 and 1.80, respectively. Approximately 23% of the patients had a previous stroke/TIA, and 72% had systemic arterial hypertension. Regarding the valve position, it was mitral in 26 patients (59.1%), aortic in eight (18.2%), and both in ten (22.7%). Data on medication use and the presence of concomitant valve diseases at baseline are provided in Table S3 and S4, respectively, in the Supplementary Appendix (see the Electronic Supplementary Material).

3.2 Drugs

Of the 44 patients who underwent randomization, 23 were assigned to receive rivaroxaban and 21 were assigned to receive warfarin. All patients in the rivaroxaban group received rivaroxaban 15 mg BID, while patients included in the warfarin group received a dose adjusted according to the INR; for the latter, the mean interval from the administration of the first dose of warfarin to the achievement of the target INR was 7 days. Patients in the warfarin group had an INR in the therapeutic range for a mean 56% of the time. The average real follow-up time of the study was approximately 95.6 days.

3.3 Primary Outcome

The efficacy and safety outcomes are summarized in Table 2. The primary outcome of stroke/TIA/SBI and SE occurred in one patient (4.3%) in the rivaroxaban group and three patients (14.3%) in the warfarin group (risk ratio [RR] 0.27; 95% confidence interval [CI] 0.02–2.85; $P = 0.25$). In the warfarin group, ischemic stroke occurred in two



CONSORT 2010 Flow Diagram. BMI: body mass index; APS: Antiphospholipid Syndrome; AE: aortic stenosis; ASA: acetylsalicylic acid; CT: Computed tomography; TEE: transesophageal echocardiography: BID: twice a day.

Fig. 1 Enrollment, randomization, and follow-up (CONSORT 2010 flow diagram)

patients (9.5%) and SBI occurred in only one patient (4.8%) (Fig. 2a). There were no cases of stroke or SBI in the rivaroxaban group, but one patient had TIA (4.3%). There were no cases of hemorrhagic, fatal, or disabling stroke in both groups tested. Among the patients with ischemic strokes, there was no identification of hemorrhagic transformation.

3.4 Key Secondary and Other Efficacy Outcomes

Stroke/TIA/SBI/SE and death from any cause occurred in one patient (4.3%) in the rivaroxaban group and four patients (19.05%) in the warfarin group (RR 0.19; 95% CI 0.02–1.89; $P = 0.12$) (Fig. 2b). Death from any cause occurred in only one patient (4.8%) in the warfarin group (RR 0.95; 95% CI 0.86–1.04; $P = 0.29$) and resulted from AMI, but the difference was not significant in both groups assessed. The echocardiographic parameters evaluated were maximum, mean, and peak pressure gradients, peak velocity, acceleration time (only aortic prostheses), effective orifice area, Doppler velocity index, and pressure half-time (evaluated only in the mitral position). The means of the differences found were not statistically significant, as detailed in Table S5 and S6 in the Supplementary Appendix (see the Electronic Supplementary Material).

Table 1 Baseline characteristics of the patients

Characteristic	Rivaroxaban ($n = 23$)	Warfarin ($n = 21$)
Female, *n* (%)	14 (60.9)	13 (61.9)
Age, mean, years	46.57 ± 10.3	42 ± 8.7
BMI, mean, kg/m^2	24.6	27.4
Type of valve-replacement surgery, *n* (%)		
Isolated mitral	12 (52.2)	14 (66.7)
Isolated aortic	6 (26.1)	2 (9.5)
Mitroaortic	5 (21.7)	5 (23.8)
Medical history		
LVEF, mean, *n* (%)	58.4 ± 9.9	54.2 ± 13.2
Creatinine clearance, mean, ml/min	104 ± 15.5	102 ± 23.5
Hypertension, *n* (%)	17 (73.9)	15 (71.4)
Smoking, *n* (%)[a]	3 (13)	2 (9.5)
Atrial fibrillation, *n* (%)	7 (30.4)	5 (23.8)
Previous rheumatic fever, *n* (%)	18 (78.3)	18 (85.7)
Prior stroke/TIA, *n* (%)	3 (13)	7 (33.3)
Previous minor bleeding, *n* (%)	7 (30.4)	3 (14.3)
NYHA class I–II, *n* (%)	22 (95.7)	20 (95.2)
Left atrium, mean, mm	76 ± 31.5	74.4 ± 28.3
HAS-BLED score[b], mean	1.7 ± 0.9	1.9 ± 1.04
CHA^2DS_2-VASc score[c], mean	2.3 ± 1.1	2.3 ± 1.19

Plus–minus values are means ± SD

No significant differences were noted between the groups

BMI body mass index, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *SD* standard deviation, *TIA* transient ischemic attack

[a]Previous or actual

[b]HAS-BLED score: Hypertension, abnormal renal/liver function, and stroke; bleeding history or predisposition, labile international normalized ratio, elderly, and drugs/alcohol. A score of ≥ 3 suggests increased bleeding risk and warrants some caution and/or regular review

[c]CHA_2DS_2-VASc score: Congestive heart failure, hypertension, and age ≥ 75 years; diabetes mellitus and stroke/TIA/thromboembolic event; vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque), age 65–74 years, and female sex. This scoring system was developed to predict the annual risk of thromboembolic events in patients with atrial fibrillation

Valve thrombosis and new intracardiac thrombus were not reported in either treatment group.

3.5 Overall Safety Outcomes

Major bleeding, intracranial hemorrhage, fatal bleeding, and clinically relevant non-major bleeding were not reported in the present study, in both groups tested. However, minor bleeding as defined according to the ISTH and BARC criteria occurred in almost equal proportions of patients in the rivaroxaban group and the warfarin group: six (26.1%) and six (28.6%), respectively (RR 0.88; 95% CI 0.23–3.32; $P = 0.85$).

4 Discussion

In the present study, we conducted a pilot randomized clinical trial with the objective of evaluating the efficacy and safety of rivaroxaban (15 mg BID), an FXa inhibitor, compared to dose-adjusted warfarin, in patients with MHVs over 90 days. We found in this study that there was no statistical difference between the rivaroxaban and warfarin groups in any outcome assessed; numerically, the rivaroxaban group had a lower proportion of events.

Table 2 Efficacy and safety outcomes, according to treatment group

Outcome	Rivaroxaban ($n = 23$)	Warfarin ($n = 21$)	Relative risk	P value
Primary efficacy outcome: stroke/TIA/SBI or SE	1 (4.3)	3 (14.3)	0.27 (0.02–2.85)	0.25
Ischemic stroke	0	2 (9.5)	0.90 (0.78–1.03)	0.13
TIA	1 (4.3)	0	1.04 (0.95–1.14)	0.33
SBI	0	1 (4.8)	0.95 (0.86–1.04)	0.29
SE	0	0	NA	NA
Key secondary efficacy outcome: stroke/TIA/SBI/SE and death (any cause)	1 (4.3)	4 (19)	0.19 (0.02–1.89)	0.12
Death from any cause	0	1 (4.8)	0.95 (0.86–1.04)	0.29
Other secondary outcomes of efficacy[a]				
Myocardial infarction	0	1 (4.8)	0.95 (0.86–1.04)	0.29
Primary safety outcome: ISTH or BARC major bleeding	0	0	NA	NA
Other secondary outcomes of safety				
Minor bleeding[b]	6 (26.1)	6 (28.6)	0.88 (0.23–3.32)	0.85

Values are number (%) unless indicated otherwise

BARC Bleeding Academic Research Consortium, *ISTH* International Society on Thrombosis and Haemostasis, *NA* denotes not applicable, *SBI* silent brain infarction, *SE* systemic embolism, *TIA* transient ischemic attack

[a]Valve thrombosis and new intracardiac thrombus have not been reported in either the rivaroxaban or warfarin groups

[b]According criteria of Control of Anticoagulation Subcommittee of the ISTH and/or HAS-BLED score and/or BARC score. All patients had minor bleeding (BARC 1)

A peculiarity of this study was the use of TEE and head CT scan at the beginning and at the end of the study, even in the absence of symptoms, in order to diagnose subclinical or asymptomatic events. The encouraging results of this study confirm the 'proof of concept' that selective FXa inhibitors can be effective in preventing the formation of clots in patients with MHVs. FXa plays a central role in blood coagulation and is activated by both the intrinsic and extrinsic coagulation pathways; besides this, it directly converts prothrombin to thrombin via the prothrombinase complex, leading to fibrin clot formation and activation of platelets by thrombin [18]. In keeping with this, Petzold et al. identified that FXa is a potent direct agonist of the protease-activated receptor 1 (PAR-1), leading to platelet activation and thrombus formation [19] .

The first report on the use of rivaroxaban in patients with MHVs was made in 2011 by Kaeberich et al., who used an in vitro model, with the objective of evaluating the effectiveness of preventing thrombus formation when using this drug in high doses (300 ng/ml = 20 mg bolus), compared to the use of unfractionated heparin (0.8 IU/ml) and low-molecular-weight heparin (0.7 IU/ml), and showed that there was no significant difference between the groups tested [9]. Subsequently, in 2014, Greiten et al. conducted an animal model study using an MHV in the aortic position, comparing rivaroxaban (at a dose of 2 mg/kg) with subcutaneous enoxaparin (2 mg/kg). In that study, rivaroxaban demonstrated greater efficacy than enoxaparin in short-term thromboprophylaxis, in addition to a greater reduction in platelet deposition on the 30th day after implantation [10]. Similarly, Lester et al. conducted an animal model study involving the use of a heterotopic aortic mechanical prosthesis and apixaban (another FXa inhibitor), and showed promising results for MHV thromboprophylaxis compared to warfarin use [20].

The RE-ALIGN study (2014), the first clinical trial involving the use of a DOAC compared to warfarin in patients with MHVs, evaluated the use of dabigatran (the only oral direct thrombin inhibitor available) at a dose of 300 mg (BID), aiming to reach a minimum serum level of 50 ng/ml. The study was stopped prematurely due to the high incidence of thromboembolic events at the expense of increased hemorrhagic outcomes in the dabigatran group compared to the warfarin group, and this was an absolute contraindication to dabigatran use in patients with MHVs [8]. It is important to highlight that the outcomes occurred mainly in the population up to 3 months postoperatively, leading to the hypothesis that the drug's mechanism of action and its ability to block the activation of the coagulation cascade is overloaded.

Unlike the RE-ALIGN study, we selected only patients with a postoperative time of ≥ 3 months, because in the first 90 days, the incidence of thromboembolic events is known to be higher, even in patients with a bioprosthesis [21]. To avoid confounding, we opted for prohibition of

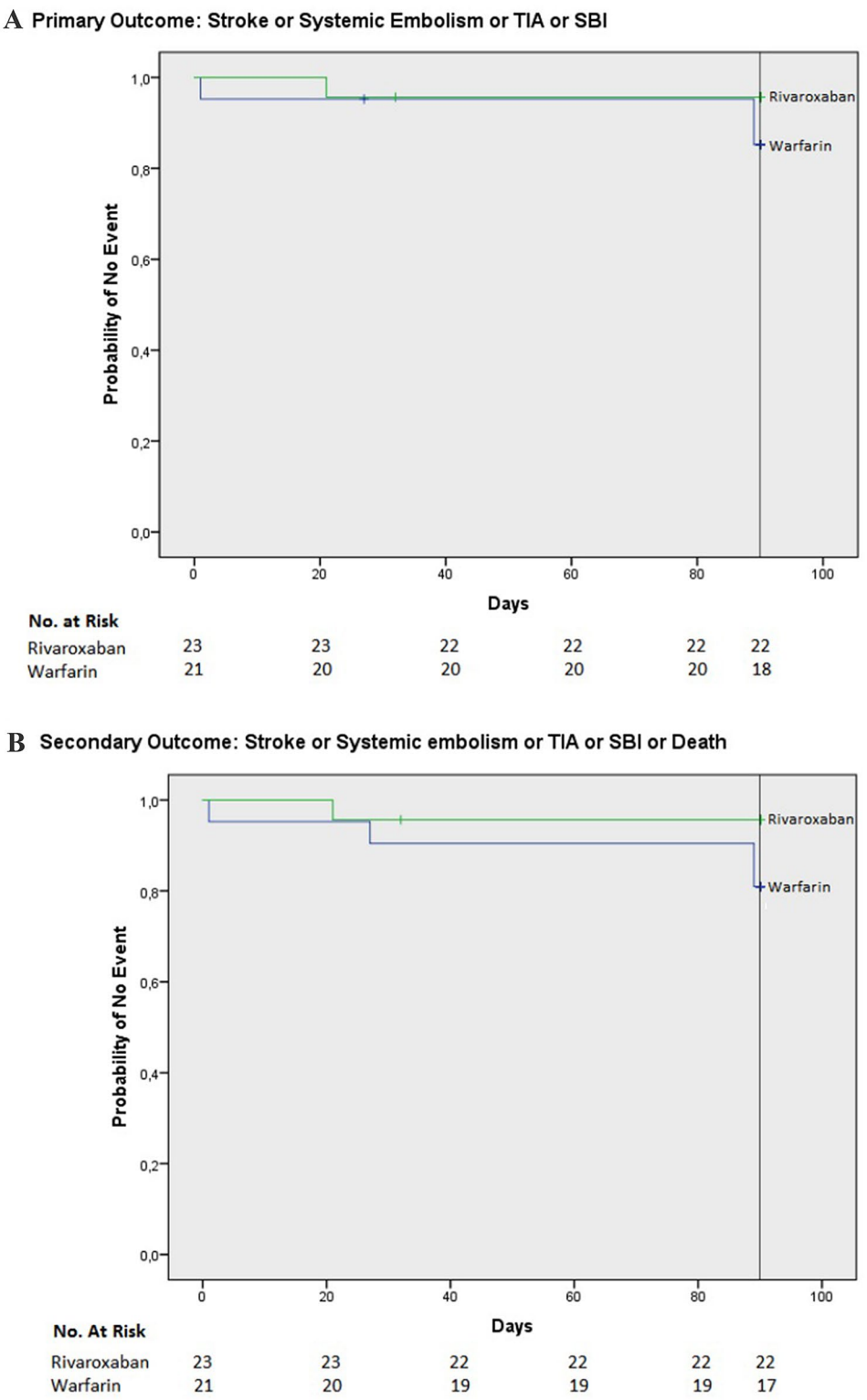


Fig. 2 Kaplan-Meier curves for the primary and secondary efficacy outcomes. The primary efficacy outcome (**a**) was stroke, transient ischemic attack (TIA), silent brain infarction (SBI), and systemic embolism. The secondary efficacy outcome (**b**) was the composite of stroke/TIA/SBI/systemic embolism and death from any cause. In each panel, the *vertical line* indicates the end of the follow-up

the use of any antiplatelet concomitant with the tested anticoagulant in both groups.

In 2018, we published the world's first human experiment using rivaroxaban in patients with MHVs. The study used a controlled before and after study design, selecting seven patients, all after isolated replacement of the mitral valve and with unstable INR, in addition to being at least 3 months postoperative. After performing TEE and CT scans, they were treated with 15 mg rivaroxaban BID, which was maintained for 90 days, when the TEE and CT

were repeated. No patient had clinical events and/or valve thrombosis and/or intracardiac thrombus with or without symptoms [22].

Recently, a study conducted in Switzerland in 2020 included ten patients at low risk for thromboembolisms with an MHV in the aortic position and a recent postoperative period. For such individuals, rivaroxaban 20 mg was administered once daily (from the third postoperative day) and maintained for 6 months. No thromboembolic or hemorrhagic events and/or deaths were observed [23].

In this study, we opted for the use of a higher dosage of rivaroxaban (15 mg BID), generally used as a loading dose in other thrombotic conditions. In addition, our sample consisted of relatively young patients with a low risk of bleeding. We believe that the sum of these factors was fundamental to obtaining encouraging results in this study. According to Chan et al., clotting on MHVs is triggered via activation of the contact system, and one molecule of FXa triggers the generation of 1000 molecules of thrombin [24], ratifying the importance of inhibiting FXa in this scenario.

4.1 Limitations

There are several limitations of the RIWA study, among which we highlight the following: unicentric pilot study, small sample size, and short follow-up (90 days) for the occurrence of major clinical events.

The greater number of patients with isolated aortic valve replacement and the smaller number of cases with previous stroke could increase the possibility of patients with lower thromboembolic risk having been randomly selected for the rivaroxaban group. However, there is also a numerical increase in patients with AF, smoking, and bleeding events in this same group, which could offset the benefits. It is important to remember that this is a proof-of-concept study. Thus, it is necessary to carry out randomized studies with the statistical power to clarify this hypothesis.

5 Conclusion

In this pilot study, rivaroxaban 15 mg twice daily had thromboembolic and bleeding events similar to warfarin in patients with mechanical heart valves. These data confirm the authors' proof-of-concept and suggest that a larger trial with a similar design is not unreasonable.

Declarations

Funding This work was supported by General Hospital Roberto Santos.

Conflict of interest The authors, ARD, YdSLB, ISS, KSOT, LVP, JALF, MGN, RAJ, and LR, declare that they have no conflict of interest.

Ethics approval The trial protocol was approved by the local ethics committee.

Consent to participate All patients provided written informed consent before enrollment.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Code availability Not applicable.

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