Usefulness and Safety of Rivaroxaban in Patients Following Isolated Mitral Valve Replacement With a Mechanical Prosthesis

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A B S T R A C T

Rivaroxaban has previously been tested in experimental and animal models with encouraging results. We prospectively selected seven patients between May 2017 and January 2018 who underwent isolated mitral valve replacement with a mechanical prosthesis and had unstable INR control at least 3 months after surgery. An intervention of rivaroxaban 15 mg was then administered twice daily for a period of 90 days. No patient presented intracardiac thrombus, reversible ischemic neurological deficit, ischemic or hemorrhagic stroke, and hospitalization or death during 3 months of follow-up. Two patients eradicated the presence of spontaneous echo contrast. Mean and peak pressure gradients, peak velocity, effective orifice area, and PHT were similar before and after the intervention. In conclusion, the use of rivaroxaban for 90 days in seven patients after replacement of mitral valve with the mechanical prosthesis did not present thromboembolic or bleeding events (NCT02894307). **(Am J Cardiol 2018;00:1−4)**

It is estimated that four million valve replacement procedures have been performed over the last 50 years, and it remains the only definitive treatment for most patients with advanced heart valve disease.[1] Due to the narrow therapeutic index, interactions, genetic variants, and need for blood monitoring of patients taking vitamin K antagonists (VKA), alternatives to warfarin have now been made available—specifically, inhibitors that directly target Factor IIa (dabigatran) or Xa (rivaroxaban, apixaban, and edoxaban).[2-4] On the other hand, rivaroxaban has already been tested in experimental[5] and animal models[6] with encouraging results.[7] According to these findings, we hypothesized that a direct Factor Xa inhibitor could be evaluated in patients with mechanical heart valves (MHV) for prevention of thromboembolic events.

Methods

Patients were selected from an original cohort of 550 subjects with MHV. From this group, we initially selected 19 patients with low-quality anticoagulation with warfarin, identified through frequent lability of INR, despite careful follow-up of the medical staff; however, 12 patients were excluded. We prospectively selected seven patients between May 2017 and January 2018 who underwent isolated mitral valve replacement with MHV and demonstrated unstable INR control—that is, poor responders to warfarin therapy—assessed by the time in therapeutic range (TTR) <50%. A modified Rosendaal method of linear interpolation was used between each pair of measured INR values.[8] The INRs outside the therapeutic range were repeated every 7 days for at least 3 months for improved TTR accuracy.[9] An intervention of rivaroxaban 15 mg was then administered twice daily for a period of 90 days (Figure 1).

Transesophageal echocardiography (TEE) to exclude subclinical valve thrombosis, spontaneous echo contrast (SEC), or intracardiac thrombus and computed tomography (CT) head scan to exclude infarction or cerebral hemorrhage were performed in all patients before and after rivaroxaban use. During follow-up, all patients were contacted weekly by telephone, and every 30 days, where they performed a transthoracic echocardiogram and a face-to-face consultation. At the end of the follow-up, the warfarin dose was adjusted to maintain the international normalized ratio (INR) from 2.5 to 3.5. SEC was defined as a dynamic smoke-like signal that swirled slowly in a circular pattern within the LA and appendage, with gradation (1 to 4+).[10] The bleeding risk was based on the criteria of Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis.[11] TEE was performed using a commercially available ultrasound imaging system (iE33; Philips Medical Systems, Andover, MA) with a three-dimensional matrix-array transesophageal transducer.

Mortality and morbidity events (reversible ischemic neurological deficit, ischemic and hemorrhagic stroke, systemic embolism, any bleeding, prosthesis valve thrombosis and death) were evaluated in an exploratory manner. The trial protocol was approved by the local ethics and research committee in the city of Salvador, Brazil (under protocol number 69327617.7.0000.5028) and Clinical Trials number NCT02894307. Written informed consent was obtained from all patients.

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See page 3 for disclosure information.

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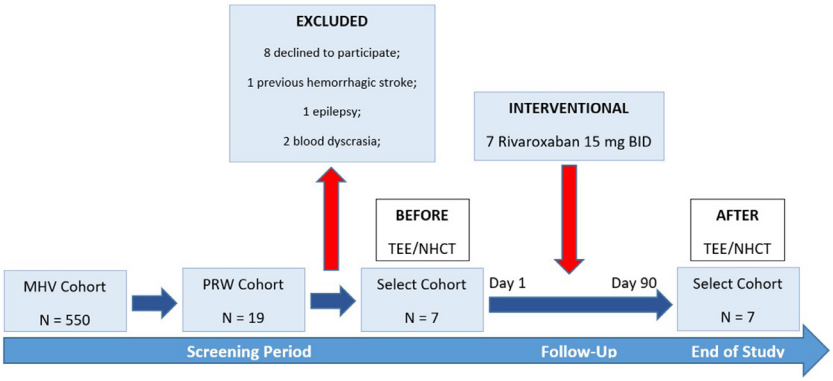

Figure 1. Flow chart of the study design. MHV = mechanical heart valve; NHCT = noncontrast head computed tomography; PRW = poor responders to warfarin; TEE = transesophageal echocardiogram.

Statistical Considerations

The SPSS 17.0 (SPSS Inc., Chicago, IL) was used to perform statistical analysis of the collected data. Quantitative variables were described as means and standard deviations. The mean comparison was performed using the Student t-test. The qualitative and categorical variables were presented as percentages and their comparisons were made by the chi-square or the Fisher exact test when indicated. Within-group variations between baseline and 90-days values were evaluated using the paired sample t-test. When appropriate, we calculated the 95% confidence interval for the observed differences. All statistical tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

After the recruitment of the seven cases, the study was suspended. There were a few patients with unstable INR and a few patients were referred for this project. Despite a high patient satisfaction index and a desire to continue with the study drug, we opted to suspend and publish the preliminary results. The characteristics of the patients at baseline are presented in Table 1.

The echocardiographic parameters evaluated were mean and peak pressure gradients, peak velocity, effective orifice area, and PHT. When comparing before and after the use of rivaroxaban, paired t-test results did not present significant differences. No patient presented intracardiac thrombus, reversible ischemic neurological deficit, ischemic or hemorrhagic stroke, and hospitalization or death. In addition, reversion of SEC occurred in two patients (Table 2).

Discussion

In patients with MHV in the mitral position who presented objective difficulty with the warfarin therapy due to unstable INR control, the use of rivaroxaban at the dose of 15 mg two times per day for 90 consecutive days demonstrated that Factor Xa inhibitors may be a viable alternative. The systematic use of CT head scan and TEE at the beginning and at the end of the study, increasing sensitivity for subclinical thromboembolic, raises the robustness of the results demonstrated. Although we have a very small sample, the intervention design was purposely used to ensure that when performing the hemodynamic assessment of the valve prosthesis with the use of echocardiogram, we guaranteed that the alterations found would not be justified by the particularity of the prostheses or by inter-individual variability.

To the best of our knowledge, our present study is the first to investigate directly an inhibitor of Factor Xa

Table 1
Baseline characteristics of the seven patients

Patient	Sex	Age (years)	AF	LVEF (%)	BMI (kg/m^2)	HAS BLED[†]	CHA_2DS_2VASc[‡]
1	F	38	No	65	21.4	2	2
2	F	38	Yes	44	29.7	3	1
3	F	40	No	58	36.4	3	2
4	M	43	No	43	27.5	3	2
5	F	45	Yes	68	29	4	3
6	F	46	Yes	68	22.5	3	2
7	F	55	Yes	52	25	4	3
Mean	-	43.5	-	56.8	27.3	3.1	2.1
Median	-	43	-	58	27.5	3	2

BMI = body mass index (kg/m^2); LVEF = left ventricular ejection fraction; AF = atrial fibrillation;

[†] HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile international Normalized Ratio, Elderly, Drugs/Alcohol. A score of ≥3 suggests increased bleeding risk and warrants some caution and/or regular review.

[‡] CHA_2DS_2VASc = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age from 65 to 74, and female sex.