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

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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;122:1047–1050)**

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 1049 for disclosure information.

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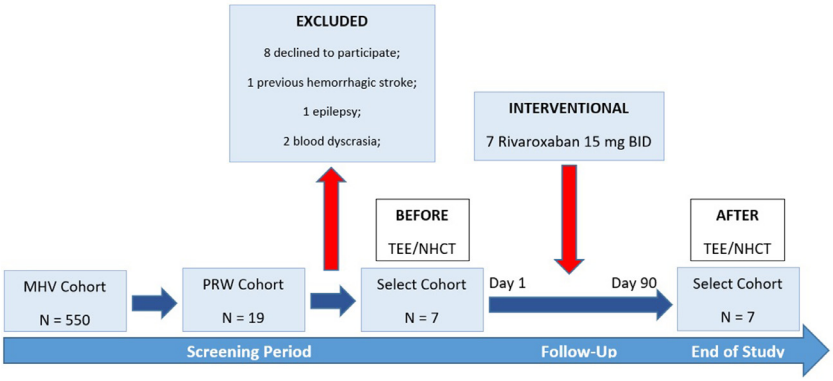

Figure 1. Flow chart of the study design. MHV = mechanical heart valve; NHCT = noncontrast head computed tomography; PRW = poor responders to warfarin; TEE = transesophageal echocardiogram.

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.

Table 2
Echocardiographic parameters before and after rivaroxaban use

Patient	Mean gradient (mm Hg)	Peak gradient (mm Hg)	Peak velocity (m/s)	EOA (cm^2)	PHT* (ms)	SEC†
Before After						
1	3.0	10	1.5	1.5	80	-
	4.0	12	1.33	1.8	77	-
2	5.0	17	2.00	1.9	59	-
	6.0	17	2.04	1.9	97	-
3	8.0	19	2.20	2.0	67	+1
	7.0	23	2.40	2.4	68	+1
4	5.0	15	1.92	2.7	64	-
	7.0	21	2.20	2.9	37	-
5	3.0	12	1.72	2.6	84	-
	4.0	17	2.04	2.5	66	-
6	4.3	8.7	1.56	2.9	59	+1
	5.0	9.0	1.41	2.9	70	-
7	4.0	11	1.65	2.0	61	+4
	2.0	6.0	1.26	3.0	72	-
Paired test: p Value	0.48	0.26	0.85	0.15	0.82	-

* PHT = pressure half-time (ms).
† SEC = spontaneous echo contrast (- not detected; +/+4 intensity).

(rivaroxaban) in patients with MHV in mitral position. A previous work that we found includes only one case report that related an unsuccessful off-label use of rivaroxaban in a patient with an MHV in aortic position with several confounders and limitations.[12] In addition, Greiten et al[6] reported for the first time the use of rivaroxaban versus enoxaparin in an animal model implanted with mechanical bileaflet aortic valve prosthesis with no complications.

The only other novel oral anticoagulant (NOAC) tested in patients with MHV was dabigatran (direct thrombin inhibitors) in RE-ALIGN[3] trial (dabigatran vs warfarin), which was terminated early when an interim analysis revealed more thromboembolic events and bleeding with dabigatran compared to warfarin. Rivaroxaban may be more effective than dabigatran for preventing thrombosis on MHVs for some reasons: first, triggering the intrinsic pathway, MHVs induce the local generation of thrombin in concentrations that exceed those of dabigatran (which inhibits thrombin in a 1:1 manner—a clinical dose of roughly 620 mg twice daily would be required to achieve concentrations high enough to inhibit thrombus formation in this scenario, making the risk of bleeding unacceptable); second, they attenuate thrombin generation (each inhibited molecule of rivaroxaban blocks the production of 1000 molecules of thrombin)[13]. In addition, NOACS are superior to warfarin for the prevention of the composite of stroke and systemic embolism in patients with AF and an additional risk factor for stroke.[14] Moreover, compared with warfarin, the rate of thromboembolism and intracranial hemorrhage in patients treated with higher dose NOACs was lower and major bleeding was similar in patients with valvular heart disease and AF.[15]

In addition, there is mounting evidence that the root cause of thrombosis on blood contacting medical devices is the activation of Factor XII. In the absence of oral inhibitors of Factor XII, oral Factor Xa inhibitors may be the next best choice.[16]

Based on this pilot study, the use of rivaroxaban for anticoagulation in patients with unstable INR following mechanical mitral valve replacement may be feasible, efficacious, and safe. However, rigorous and larger randomized clinical trials need to evaluate this further before it is adopted as an alternative to warfarin in this patient population.

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Disclosures

The authors have no conflicts of interest to disclose.

1. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet* 2009;374:565–576.
2. Mega JL, Simon T. Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments. *Lancet* 2015;386(9990):281–291.
3. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper K, Khder Y, Lobmeyer MT, Maas H, Voigt J, Simoons ML, Werf FV. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206–1214.
4. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR, Danielson GK, Orszulak TA, Pluth JR, Puga FJ, Schaff HV, Jeffrey BS, Larsonkeller JJ. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. *J Am Coll Cardiol* 1995;25:1111–1119.
5. Kaeberich A, Reindl I, Raaz U, Maegdefessel L, Vogt A, Linde T, Steinseifer U, Perzborn E, Hauroeder B, Buerke M, Werdan K, Schlitt A. Comparison of unfractionated heparin, low-molecular-weight heparin, low-dose and high-dose rivaroxaban in preventing thrombus formation on mechanical heart valves: results of an in vitro study. *J Thromb Thrombolysis* 2011;32:417–425.
6. Greiten LE, McKellar SH, Rysavy J, Schaff HV. Effectiveness of rivaroxaban for thromboprophylaxis of prosthetic heart valves in a porcine heterotopic valve model. *Eur J CardiothoracSurg* 2014;45:914–919.
7. Aramendi JI, Mestres CA. Initial experience with rivaroxaban in mechanical valve prosthesis in an animal model. *Eur J CardiothoracSurg* 2014;45:920–921.

8. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb-Haemost* 1993;69:236–239.
9. Reiffel JA. Time in the therapeutic range for patients taking warfarin in clinical trials: useful, but also misleading, misused, and overinterpreted. *Circulation* 2017;135:1475–1477.
10. Fatkin D, Kelly RP, Feneley MP. Relations between left atrial appendage blood flow velocity, spontaneous echocardiographic contrast and thromboembolic risk in vivo. *J Am Coll Cardiol* 1994;23:961–969.
11. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. . Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–694.
12. Kumar V, Kelly S, Raizada A, Yee J, Anuwatworn A, Stys A, Stys M. Mechanical valve thrombosis on rivaroxaban: are novel anticoagulants really an option? *Methodist Debakey Cardiovasc J* 2017;13(2):73–75.
13. Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. *J Am Coll Cardiol* 2016;68:2670–2689.
14. Hicks T, Stewart F, Eisinga A. NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis. *Open Heart* 2016;3(1):e000279.
15. Renda G, Ricci F, Giugliano RP, De Caterina R. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and valvular heart disease. *J Am Coll Cardiol* 2017;69:1363–1371.
16. Chan NC, Weitz JI, Eikelboom JW. Anticoagulation for mechanical heart valves: will Oral Factor Xa inhibitors be effective. *Arterioscler Thromb Vasc Biol* 2017;37:743–745.