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A Randomized Clinical Trial to Evaluate the Efficacy and Safety of Rivaroxaban in Patients with Bioprosthetic Mitral Valve and Atrial Fibrillation or Flutter: Rationale and Design of the RIVER Trial

Short title: RIVER Trial: Rationale and Design

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ABSTRACT

Background: The efficacy and safety of rivaroxaban in patients with bioprosthetic mitral valves and atrial fibrillation or flutter remain uncertain.

Design: RIVER was an academic-led, multicenter, open-label, randomized, non-inferiority trial with blinded outcome adjudication that enrolled 1005 patients from 49 sites in Brazil. Patients with a bioprosthetic mitral valve and atrial fibrillation or flutter were randomly assigned (1:1) to rivaroxaban 20 mg once daily (15 mg in those with creatinine clearance <50 mL/min) or dose-adjusted warfarin (target international normalized ratio 2.0–30.); the follow-up period was 12 months. The primary outcome was a composite of all-cause mortality, stroke, transient ischemic attack, major bleeding, valve thrombosis, systemic embolism, or hospitalization for heart failure. Secondary outcomes included individual components of the primary composite outcome, bleeding events, and venous thromboembolism.

Summary: RIVER represents the largest trial specifically designed to assess the efficacy and safety of a direct oral anticoagulant in patients with bioprosthetic mitral valves and atrial fibrillation or flutter. The results of this trial can inform clinical practice and international guidelines

INTRODUCTION

Valvular heart disease affects more than 100 million people worldwide[1] and is a growing problem due to rheumatic heart disease in low- and middle-income countries and degenerative valve disease in the aging population in high- and middle-income countries.[1,2] In Brazil, valvular heart disease is one of the leading causes of cardiovascular hospitalizations.[3,4] Mitral insufficiency and stenosis, usually secondary to rheumatic fever, are the most common forms of valvular heart disease in Brazil.[3,4] In high-income countries, prolapse and degeneration are the primary reasons for mitral valve surgery.[5-7]

Replacement of the diseased native valve with a prosthetic valve is the main treatment option for patients with severe valvular heart disease.[5-7] Over 4 million people worldwide have received a prosthetic valve, and an estimated 300,000 valves are implanted every year.[8,9] Prosthetic valves improve survival and quality of life in patients with severe valvular heart disease, however, they can be associated with an increased risk of thrombotic events.[10-13] A systematic review found rates of valve thrombosis of 1.8/100 patient-years, major embolism of 4.0/100 patient-years, and total embolism of 8.6/100 patient-years.[12] The risk of thromboembolism is highest in the 3 months after bioprosthetic valve surgery in uncomplicated patients[5,10-13]; however, the risk persists indefinitely in those with atrial fibrillation (AF).[7,10-13] Atrial fibrillation in the setting of mitral valve disease is common, with an occurrence of 30% to 40%.[14-16]

Due to the risk of thrombotic events, lifelong use of oral anticoagulants is indicated for patients in sinus rhythm with mechanical heart valves, regardless of other medical conditions. Among patients with bioprosthetic heart valves, lifelong anticoagulation is particularly recommended if they have atrial fibrillation.[5,9,17-25] There is limited evidence from randomized trials on the use of oral anticoagulation with vitamin K antagonists (VKAs) in patients with bioprosthetic heart valves.[22,25]

Recommendations for Antithrombotic Therapy for Patients with Bioprosthetic Valves

The current recommendation for antithrombotic therapy in patients with bioprosthetic valves is aspirin 75–100 mg per day.[2,3,5,23-26] The use of VKAs for 3–6 months after bioprosthetic mitral valve replacement

(MVR) is recommended for patients at low risk of bleeding, based mainly on evidence from non-randomized trials.[27-29] Anticoagulation early after valve implantation is intended to decrease the risk of thromboembolism until the prosthetic valve is fully endothelialized. The level of anticoagulation was assessed in a small randomized trial that indicated a better net benefit with a less intensive regimen of anticoagulation.[22] The use of a direct oral anticoagulant (DOAC) primarily related to the mitral procedure, regardless of the existence of AF, was assessed in 220 patients in the ENAVLE trial.[30] This trial found that edoxaban was non-inferior to VKA in the first 3 months after mitral or aortic surgery (repair or bioprosthetic valve implantation). Routine anticoagulation is recommended for a limited period of time; however, this recommendation is based mainly on non-randomized trials with small sample sizes.

Despite the standard recommendation of anticoagulation for 3–6 months after surgery, there are instances in which lifelong use of anticoagulant therapy is recommended. Regardless of the timing of surgery, patients with a bioprosthetic valve or mitral repair and AF are at higher risk for embolic events and should use anticoagulants irrespective of their CHA_2DS_2-VASc score.[3,5,24,27,31,32] The RIVER trial is designed to assess the use of DOACs in patients with atrial flutter or fibrillation and bioprosthetic mitral valves with an indication for lifelong use of anticoagulants. The evidence on the use of DOACs in this population is mainly from subgroup analyses in small numbers of patients from pivotal trials.[33,34] Larger studies are needed to determine the safety and efficacy of DOACs in patients with AF and bioprosthetic heart valves.

Evidence for Rivaroxaban in Atrial Fibrillation

Rivaroxaban, an oral, direct factor Xa inhibitor, is recommended for the prevention and treatment of thromboembolic disorders.[31,32,35-37] Due to a more consistent anticoagulant effect, which is less influenced by food or concomitant medications, rivaroxaban is an effective and safe alternative to warfarin for patients with AF.[31,32,35-37] The primary evidence supporting the use of rivaroxaban in patients with atrial fibrillation is from the ROCKET AF trial.[37] In ROCKET AF, 14,264 patients with nonvalvular AF were randomized to receive 20 mg rivaroxaban once daily (15 mg in those with moderate renal impairment at screening) or dose-adjusted warfarin (target international normalized ratio [INR] 2.0–3.0). The primary

per-protocol analysis showed that rivaroxaban was non-inferior to warfarin, with 1.7 events/100 patient-years in the rivaroxaban arm compared with 2.2 events/100 patient-years in the warfarin-treated patients ($p<0.001$ for non-inferiority). Overall results were consistent in the intention-to-treat analysis. The safery endpoints of major and nonmajor clinically relevant bleeding occurred in 14.9% per year in the rivaroxaban group and 14.5% per year in the warfarin group (hazard ratio [HR] 1.03; 95% confidence interval [CI] 0.96–1.11; p=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003) in the rivaroxaban group compared with the warfarin group.

The available pre-clinical and clinical evidence supports the evaluation of rivaroxaban as a potential alternative to VKAs in patients with AF and bioprosthetic heart valves.[31,32,35-37] Despite the consistent findings, patients with bioprosthetic mitral valves were excluded from ROCKET AF.[37] Thus, we propose a multicenter, randomized clinical trial to assess the efficacy and safety of rivaroxaban compared to warfarin in patients with AF or flutter and bioprosthetic mitral valves.

METHODS

Study Design

RIVER (NCT02303795) was an academically led, investigator-initiated, multicenter, randomized, non-inferiority, open-label with blinded-endpoint adjudication trial in 1005 patients from 49 sites in Brazil.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. This was an investigator-initiated study with financial support from the Brazilian Ministry of Health (PROADI-SUS Program) and Bayer. The funding sources had no role in the study conduct, analysis, interpretation of data, or decision to publish the results.

The study was divided into a screening period, a treatment period, and a 24-hour post-treatment safety assessment (Figure 1).

The following suggestion was shared with investigators for patients transitioning from VKA to rivaroxaban in the beginning of the trial and from rivaroxaban to VKA at the end of the trial. For patients

using VKA who were randomized to rivaroxaban, study drug was started when the INR was ≤2.5. When the INR was >2.5, a new INR was measured in 1–3 days until it was ≤2.5 so rivaroxaban could be initiated. At the end of study, anticoagulation with VKA was the expected treatment for patients who were on rivaroxaban, following the standard approach of starting warfarin and only stopping rivaroxaban when the INR was ≥2.0.

The post-treatment observation period was a follow-up to record adverse events or outcomes occurring within 24 hours after the last study visit. Follow-up could be performed via telephone contact and did not require an in-person visit.

Primary Objective

The primary objective of RIVER is to assess whether rivaroxaban is non-inferior to warfarin in patients with atrial fibrillation or flutter and bioprosthetic mitral valves with respect to major clinical events at 12 months. Major clinical events were defined as a composite outcome of all-cause mortality, stroke, transient ischemic attack (TIA), major bleeding, valve thrombosis, systemic embolism, or hospitalization for heart failure. These events were selected in order to assess the net clinical benefit of the intervention, since all of the endpoints could be affected positively or negatively by the use of anticoagulation. Hospitalization for heart failure was included as a component of the composite endpoint since most clinical events monitored in RIVER may lead to heart failure decompensation (e.g., stroke, bleeding, valve thrombosis); however, some of these events may not be detected by the investigator or meet all of the criteria to be classified as one of the other endpoints included in the analysis. Therefore, monitoring heart failure hospitalization would avoid missing these events. If two concomitant events (e.g., valve thrombosis that lead to heart failure hospitalization) occur, only one event will be counted in the primary composite outcome.

Eligibility

The main inclusion criteria were age ≥18 years; paroxysmal, permanent, or persistent atrial fibrillation or flutter; and a bioprosthetic mitral valve with planned or current use of oral anticoagulation for the prevention of thromboembolism.

The risk of thrombosis is higher in mitral bioprosthesis compared with aortic bioprosthesis. We decided to study patients with bioprosthetic mitral valves in the RIVER trial because there are many questions about the use of DOACs in this population,[38] and our analysis would allow for the assessment of the effect of the intervention in a population with a higher risk of events.

Patients were considered to be eligible for enrollment 48 hours after mitral valve surgery with no limitations on timing from the 48-hour post-surgery period to randomization. Thus, patients who underwent mitral implantation of bioprosthetic valve any time in the past were eligible. Patients with or without prior exposure to oral anticoagulation were eligible. Main exclusion criteria were contraindications to the study drugs, other factors leading to excessive hemorrhagic risk, transient AF caused by a reversible disorder, and mechanical valves. Detailed inclusion and exclusion criteria are summarized in Table 1.

Randomization and Allocation Concealment

Eligible patients were randomized to receive rivaroxaban or dose-adjusted warfarin (titrated to a target INR of 2.0 to 3.0) in a 1:1 ratio in permuted blocks of 4 and were stratified according to site using a central concealed, web-based, automated, randomization system developed by the Research Institute HCor (São Paulo, Brazil).

Trial Interventions

Patients assigned to rivaroxaban received 20 mg once daily; however, those with a calculated creatinine clearance (CrCl) of 30–49 mL/min/1.73m^2 received a reduced dose of 15 mg once daily. The dose of rivaroxaban remained the same throughout the study unless there was a change in the CrCl measurement

that would necessitate a dose modification. The dose adjustment of rivaroxaban was bidirectional with changes in CrCl and could be modified at each visit or in accordance with monitoring of CrCl variation. If a patient was randomized to rivaroxaban but was using a VKA pre-randomization, investigators were instructed to start rivaroxaban at the time of the next dose of VKA if the INR was <3.0.

In patients assigned to warfarin, doses were titrated to maintain a target INR of 2.0–3.0. Among patients not using warfarin, the starting dose in the VKA arm was determine according to age. In patients >65 years old, the initial warfarin dose is 2.5 mg daily; all other patients should take 5 mg daily. INR was measured at least every 4 weeks. More frequent INR measurements were allowed according to clinical judgement or when the therapy was initiated. An unblinded physician, not affiliated with the conduct of the study, monitored the warfarin management to ensure clinical sites would respond to values out of range according to a pre-established algorithm. All patients were educated about potential drug interactions, diet, and the importance of INR measurements.

Co-Interventions

Medical

Concomitant use of aspirin up to 100 mg/day was permitted in accordance with evidence-based treatment guidelines for patients with AF and atherosclerotic disease. Thienopyridines or other antiplatelet therapy was not permitted for 5 days before randomization and fibrinolytic therapy was not permitted for 10 days before randomization. Patients who underwent vascular interventions could receive dual antiplatelet therapy with aspirin and thienopyridine at the investigator's discretion. Chronic use of nonsteroidal anti-inflammatory drugs, defined as daily use for >2 weeks, was prohibited. Specific strong cytochrome P450 3A4 inhibitors and inducers were also prohibited.

Surgical

For elective procedures, the recommendation was that most patients should stop warfarin 4 days before the planned procedure and rivaroxaban 24 hours before the procedure if renal function is normal. INR

measurements should be performed daily and patients may undergo procedures when the values are deemed appropriate by the treating physician. Bridging with parenteral (e.g., subcutaneous) antithrombotic agents was allowed. For semi-urgent procedures, the study drug was stopped and INR testing was recommended. If possible, the procedure was delayed for 24 hours which is usually enough time to reduce the risk in the rivaroxaban group in those with normal renal function. In the VKA arm, intravenous vitamin K could be used in cases of high-risk urgent procedures to reduce the level of INR. For some specific procedures (e.g., urgent percutaneous coronary intervention [PCI]), use of study drug could be continued without interruption. In the periprocedural period, INR tests were recommended as necessary. For all procedures, the recommendation was that the study drug should be resumed when hemostasis was achieved and the treating physician considered oral anticoagulant therapy to be appropriate. Bleeding complications should be treated with hemodynamic stabilization (if necessary), local treatment at the site of the bleeding, intravenous vitamin K for the VKA group, and the use of therapies to reduce the effect of anticoagulation in more severe refractory cases. Prothrombin complex concentrate (PCC) was the preference for the more severe cases in both groups, but the decision was based on local availability. A detailed report of major bleeding events after adjudication is included as a planned sub-analysis of the RIVER trial.

Trial Procedures and Follow-up

Initial baseline assessments include demographics, cardiovascular risk factors, relevant medical history, clinical characteristics, and laboratory data. After the screening, randomization, and baseline assessment visits, the other follow-up visits were schedule at 30 days and at every 3 months thereafter to identify safety and efficacy outcomes, procedures, and assessment of vital status.

Despite the controlled environment of the clinical trial, cross-over may occur in cases of potential transient or permanent contraindication to rivoraxaban (e.g., valve replacement by mechanical bioprotheses during follow-up). Imaging tests during follow-up were performed based on symptoms or routine practices at an investigator's institution. The total follow-up period was 12 months.

Outcomes

The primary outcome was a composite of all-cause mortality, stroke, TIA, major bleeding, valve thrombosis, systemic embolism, or hospitalization for heart failure. Detailed definitions for each outcome are described in the Supplementary Appendix.

Secondary efficacy outcomes included the composite outcome of disabling strokes, TIA, major bleeding, all-cause death, valve thrombosis and non-central nervous system systemic embolism, or hospitalization due to heart failure at 12 months. Venous thromboembolism and non-major bleeding were also reported as secondary outcomes at 12 months. Deaths were adjudicated as cardiovascular and non-cardiovascular. The secondary safety outcomes were bleeding events (major, minor, minimal, or fatal). Bleeding events were classified based on a specific study definition but also using the Thrombolysis in Myocardial Infarction (TIMI) and Bleeding Academic Research Consortium (BARC) criteria (Supplementary Appendix).

All potential endpoints that could be affected positively or negatively by the use of anticoagulation were included in order to assess the net clinical benefit of rivaroxaban. In addition, previous trials of DOACs have explored the effects in "broader" endpoints such as all-cause death, all-cause hospitalization, specific cardiovascular death, or cardiovascular hospitalizations. Finally, the interpretation of our randomized controlled trial will be based on the primary and secondary endpoints that capture different aspects of the patient's evolution during follow-up. Fatal events, thromboembolic events, bleeding events, valve thrombosis, and cardiovascular hospitalizations will all be reported in this trial

In the RIVER trial, an independent clinical events classification committee (CEC) has developed the CEC Charter that details, among other operational features, all steps taken to guarantee the adjudicators were blinded to treatment assignment. Since this study was not double-dummy, medication was given in an open-label setting and the INR exams also were open to the investigator in order to adjust the dose of warfarin. Since this test could expose the probable arm in the study, the clinical events classification committee was blinded to study drug and INR results were redacted in source documents.

Statistical Analysis

Main analyses will follow the intention-to-treat principle, evaluating all randomized patients according to the randomization. Categorical variables will be presented as relative and absolute frequencies. Continuous variables will be summarized using means and standard deviation or median and interquartile range.

Results for the primary outcome will be reported as Restricted Mean Survival Time (RMST).[39-42] The RMST represents the mean time free from an outcome event adjusted for losses to follow-up, reflecting the area under the survival curve. In this case, the treatment effect is estimated as the difference between groups in the RMST over the 12-month follow-up period.

Time to the occurrence of primary outcome and secondary outcomes will be expressed as Kaplan-Meier survival curves. In this case, the treatment effects are expressed as HRs derived from the Cox regression. The 95% CIs will be estimated for all efficacy measures. A per-protocol analysis, which includes all patients who received at least 1 dose of a study drug and did not have a major protocol violation, will be also performed. All statistical analyses will be performed with the use of the latest version of R software. Subgroup analyses include age, sex, time in therapeutic range, concomitant antiplatelet use, time from mitral valve implantation, type of mitral valve replacement procedure, renal function, and dose of rivaroxaban.

Sample Size

The sample size was calculated considering the primary RMST analysis, assuming a time point of 365 days. Considering a control group event rate of 14.5% with a HR of 0.79 for the primary end point and a one-sided significance level of 2.5%, a sample of 1000 patients provides approximately 80% power to detect a non-inferiority margin of 8 days favoring warfarin. When the trial was designed, there were no reliable data assessing the effects of DOACs in patients with AF and bioprosthetic valves. Therefore, we estimated the effect size based on the ROCKET AF trial,[37] which was the best available evidence with rivaroxaban, and the event rates were complemented by unpublished data from institutional databases in

Brazil. A RMST difference of 8 days (which is approximately 2% of 365 days) was deemed an appropriate non-inferiority margin by the executive committee (FIGURE 2). A similar threshold has been used previously in cardiovascular trials.[43]

Additional Pre-specified Analyses

A network meta-analysis is planned including information from other trials that addressed the outcomes in the population of patients with AF and bioprosthetic heart valves.[33,34,41] A comprehensive analysis of valvular complications including clinical and echocardiographic findings is also planned with the data from the RIVER trial. Finally, other sub-analyses will be also be performed, including results based on recurrent events, valve thrombosis, and a detailed description of cause of death and bleeding events. These additional pre-specified analyses may be reported as separate substudies of the RIVER trial.

ORGANIZATIONAL STRUCTURE

Trial Oversight

An academic steering committee designed the RIVER trial independently and, together with an operations committee from the Research Institute—Heart Hospital (HCor) (São Paulo, Brazil), oversaw the medical, scientific, and operational conduct of the study. The study also has intellectual and scientific support from a local cardiology society (Sociedade de Cardiologia do Estado de Sao Paulo [SOCESP]).

The Research Institute—HCor coordinated data management in which information from the electronic clinical report form and the clinical events committee was entered into separate databases. Source data verification, validation, and consistency checks were also performed by Research Institute—HCor. Steering committee members are responsible for the reporting of the results and for drafting and editing of this and forthcoming manuscripts.

An independent and external data monitoring committee (DMC) monitors safety data on an ongoing basis and has access to unblinded data. An independent CEC Committee, whose members were blinded to treatment assignment, adjudicated all potential primary and secondary end points.

Ethical Aspects

The study adhered to the ethical principles of the Declaration of Helsinki, specifications of the International Conference of Harmonization, and Good Clinical Practice. The study protocol was approved by an independent ethics committee or institutional review board at participating sites. The protocol required that each patient provide informed consent before initiating any study procedure.

DISCUSSION

The optimal anticoagulation strategy for patients with AF and bioprosthetic valves remains uncertain. Recent substudies from large-scale trials have reported specific findings of the effects of apixaban and edoxaban in this patient population.[33,34,44] More recently, a randomized trial comparing a DOAC with warfarin after surgical bioprosthetic valve replacement suggested noninferiority of edoxaban to VKAs.[30]

In the ARISTOTLE trial,[45] 104 (0.6%) of the 18,201 included patients had a history of bioprosthetic valve replacement (n=73 [aortic], n=26 [mitral], n=5 [mitral and aortic]) and 52(0,3%) had a history of valve repair (n = 50 [mitral], n = 2 [aortic]). Among patients with bioprosthetic valves,[33,44] 55 were randomized to apixaban and 49 to warfarin. Overall clinical event rates were low, with no significant differences between apixaban and warfarin for any outcomes.

The ENGAGE AF-TIMI 48[34,46] trial, which compared edoxaban with warfarin in patients with AF, did not exclude patients with bioprosthetic valves, thus providing an opportunity to analyze this high-risk subgroup. Of the 21,105 patients enrolled, 191 (0.9%) had previous bioprosthetic valve implantation (n=131 [68.6%] mitral, n=60 [31.4%] aortic). Rates of major bleeding were similar for the higher dose of edoxaban (60 mg) versus warfarin but were lower with lower dose of edoxaban (30 mg) versus warfarin (0.76%/year vs. 6.27%/year; HR 0.12; 95% CI 0.01–0.95; p=0.045). Patients with bioprosthetic heart valves treated with the higher dose of edoxaban had significantly lower rates of the primary net clinical outcome (7.53%/year vs. 15.77%/year; HR 0.46; 95% CI 0.23–0.91; p=0.03) and myocardial infarction, stroke, or cardiovascular death (4.32%/year vs. 11.07%/year; HR 0.36; 95% CI 0.15–0.87; p=0.03).

Patients with bioprosthetic heart valves treated with the lower dose of edoxaban had lower rates of the primary net clinical outcome (7.03%/year vs. 15.77%/year; HR 0.43; 95% CI 0.21–0.88; p=0.02).

Beyond subanalyses from pivotal trials, patients with AF and bioprosthetic valves using DOACs were also assessed in observational studies of patients with acquired and congenital heart diseases.[47,48] Overall, these studies indicated the main reasons for replacing warfarin with a DOAC were due to lack of compliance and subtherapeutic INR range. This selected group of patients had a low mean annual incidence of thromboembolism and major bleeding (both around 1%). These real-world data corroborated subanalyses from previous trials demonstrating that DOAC therapy seems effective and safe for patients with AF and a bioprosthetic valve. However, since the sample size is relatively small and this population was not randomized, the data is hypothesis generating.

The ENAVLE trial,[30] presented at 2020 American College of Cardiology Scientific Session (ACC.20)/World Congress of Cardiology (WCC), included 220 patients who had undergone successful surgical bioprosthetic valve implantation or repair to the mitral valve, aortic valve, or both. Patients were randomly assigned to receive either edoxaban (60 mg once daily or 30 mg in those with a CrCl 30–50 mL/min or with body weight ≥60 kg) or warfarin (dose adjustment to maintain INR 2.0–3.0) for 3 months. The primary efficacy outcome was a composite of death, clinical thromboembolic events, or asymptomatic intracardiac thrombosis. Rates of the primary outcome were 0% in the edoxaban group and 3.67% in the warfarin group ($p < 0.001$ for noninferiority). The primary safety outcome of major bleeding occurred in 3 patients (2.75%) in the edoxaban group and 1 (0.92%) in the warfarin group (intracranial hemorrhage) (p=0.013 for noninferiority). Of note, not all included patients had AF. Therefore, the indication for anticoagulation could have been related to the mitral procedure alone.

Limitations

The initial dose of 2.5 and 5 mg used in the warfarin arm was based on a standard adopted by the majority of the sites included in the study. Nevertheless, the potential disadvantage of this approach compared with more aggressive schemes of anticoagulation in terms of embolic protection may be counterbalanced by

less bleeding, which is a common complication in the initial phase of anticoagulation. Also, most patients randomized to the VKA arm were already using warfarin and did not need this initial dose. Other aspects to be considered include the fact that the RIVER trial assessed only one DOAC (rivaroxaban) and will not include patients with aortic bioprosthetic valves. Nevertheless, the results in pivotal trials of DOACs were very consistent among the different types of DOACs and the main concern related to these drugs is in the scenario of mitral bioprosthetic valves,[38] where the risk of thrombosis is higher. Thus, the results of the RIVER trial could have a broader application.

Conclusion

To the best of our knowledge, RIVER represents the largest randomized trial to date specifically designed to assess the efficacy and safety of a direct oral anticoagulant in patients with bioprosthetic mitral valves and atrial fibrillation or flutter. The results of this trial can inform clinical practice and international guidelines.

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FIGURE LEGENDS

Figure 1. River Trial - Study Design (screening period, treatment period, and post-treatment observation period)

Figure 2. Illustration and interpretation of non-inferiority boundaries, considering the 95% bilateral confidence intervals for the difference in restricted mean survival time between study groups (Rivaroxaban - Warfarin)

A- If the confidence interval crosses the non-inferiority margin and the upper limit of the interval confidence interval is greater than 0, then the non-inferiority of rivaroxaban compared with warfarin was not met and the results are inconclusive. B. The non-inferiority of Rivaroxaban when compared with warfarin will be demonstrated if the lower limit of the confidence interval does not cross the stipulated non-inferiority margin (8-day difference). C. Rivaroxaban will be considered superior to warfarin if the lower limit of the confidence interval is greater than 0. D. If the upper limit of the confidence interval is less than 0, then rivaroxaban will be declared inferior to warfarin.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria
1. Age ≥18 years at the time of inclusion;
2. Patients with paroxysmal, permanent, or persistent atrial fibrillation or flutter and biological prosthesis of the mitral valve,* with planned or current use of oral anticoagulants for prophylaxis of thromboembolism;
3. The patient (or legal representative) must be able to give informed consent in accordance with ICH GCP guidelines and local legislation and/or regulations.
Exclusion Criteria
1. Presence of thrombus or cardiac tumor;
2. Active endocarditis;
3. Uncontrolled hypertension (SBP >180 mm Hg and/or DBP >100 mm Hg according to measurement performed at the beginning of the study;
4. Active internal bleeding;
5. History of, or condition associated with, increased risk of bleeding, including: - Major non-cardiac surgical procedure or trauma 30 days before randomization; - Clinically significant gastrointestinal bleeding 6 months before randomization; - History of non-traumatic intracranial, intraocular, medullary or intra-articular hemorrhage; - Chronic hemorrhagic disorder; - Known intracranial neoplasia, arteriovenous malformation or aneurysm; - Planned invasive procedure with the potential for uncontrolled bleeding, including major surgery;

6. History of previous thrombotic or thromboembolic event with a high risk of bleeding:

   -Severe and disabling stroke (modified Rankin score of 4-5 inclusive) in the last three months before randomization;

   - Acute thromboembolic events or thrombosis (venous / arterial) within 14 days before randomization (e.g. acute myocardial infarction within 14 days before randomization).

7. Treatment with:

   - ASA at doses >100 mg or double antiplatelet therapy within 5 days before randomization;

   - Intravenous antiplatelet agent 5 days before randomization;

   - Fibrinolytics 10 days before randomization

   - Early need for long-term treatment with a non-steroidal anti-inflammatory;

   - Systemic treatment with a potent cytochrome P450 3A4 inhibitor, such as ketoconazole or protease inhibitors, 4 days before randomization or planned treatment during the study period;

   - Treatment with a potent cytochrome P450 3A4 inducer, such as rifampicin, phenytoin, phenobarbital or carbamazepine, 4 days before randomization or planned treatment during the study period;

8. Anemia (hemoglobin level below 7.5 g/dL) at the screening consultation;
9. Pregnancy or breastfeeding or women of childbearing age without using an effective contraceptive method;
10. CrCl calculated below 30 mL/min at the screening visit;
11. Significant liver disease identified (e.g., acute clinical hepatitis, active hepatitis, cirrhosis) or alanine aminotransferase > 3 × above the normal upper

limit;

12. Previous participation in the study.

* Patients are eligible to be included in the RIVER study and any period after 48 hours of mitral valve surgery. Thus, both patients who have undergone procedures could be included: those who are in the postoperative period (> 48h after surgery) and those who have undergone surgery a few years ago. Both patients with or without exposure to prior oral anticoagulation were eligible.

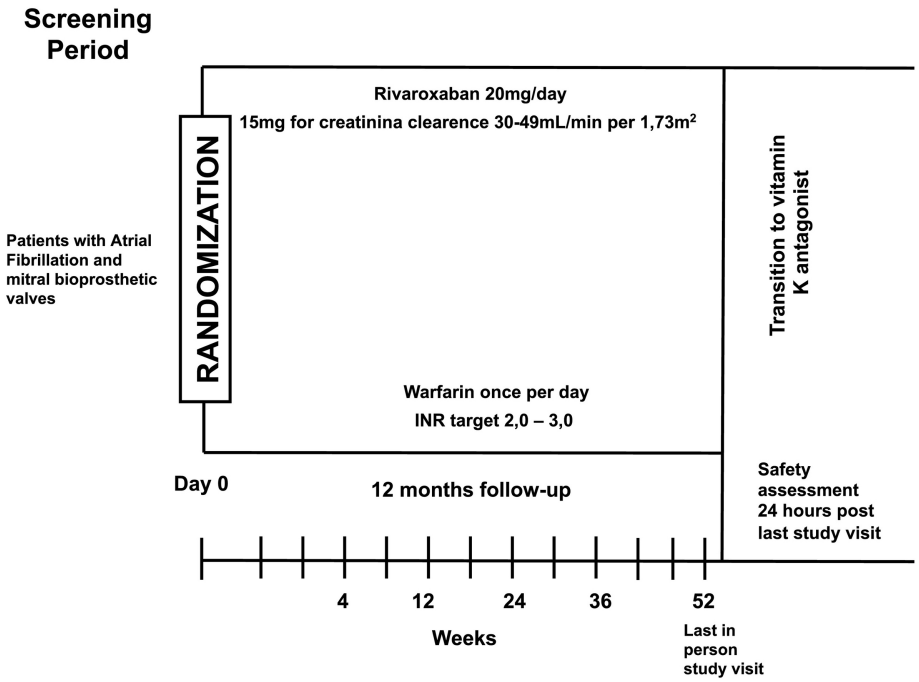
Screening Period
Patients with Atrial Fibrillation and mitral bioprosthetic valves
RANDOMIZATION
Rivaroxaban 20mg/day
15mg for creatinina clearence 30-49mL/min per 1,73m2
Warfarin once per day
INR target 2,0 – 3,0
Transition to vitamin K antagonist
Day 0
12 months follow-up
Safety assessment 24 hours post last study visit
4
12
24
36
52
Weeks
Last in person study visit

Figure 1

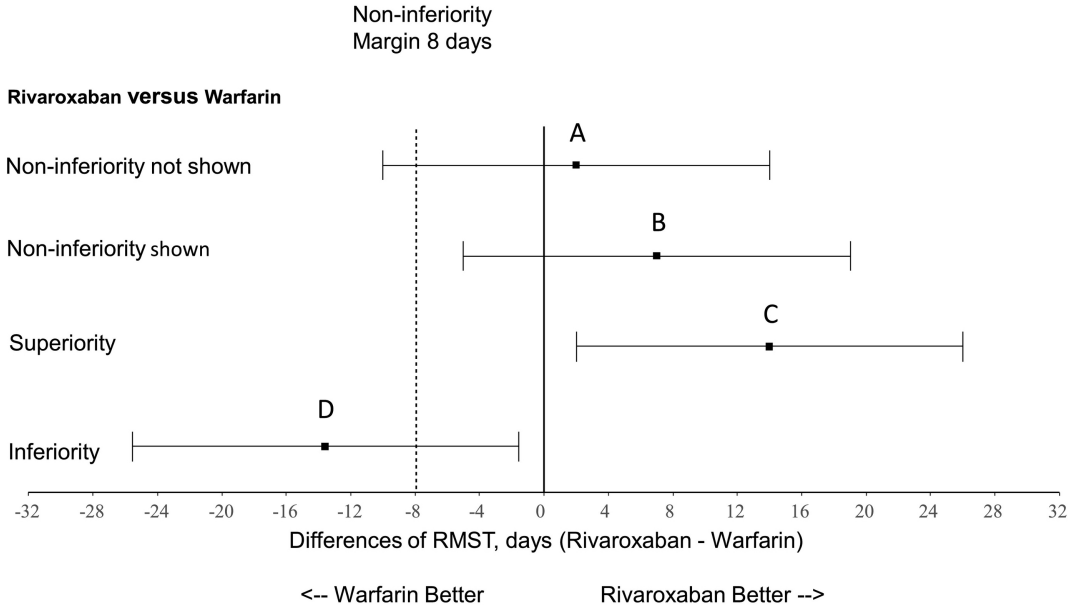
Non-inferiority
Margin 8 days
Rivaroxaban versus Warfarin
A
Non-inferiority not shown
B
Non-inferiority shown
C
Superiority
D
Inferiority
-32 -28 -24 -20 -16 -12 -8 -4 0 4 8 12 16 20 24 28 32
Differences of RMST, days (Rivaroxaban - Warfarin)
<-- Warfarin Better
Rivaroxaban Better -->

Figure 2