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ORIGINAL RESEARCH ARTICLE

Rivaroxaban versus Warfarin in Patients with Mechanical Heart Valve: Rationale and Design of the RIWA Study

André R. Durães[1,2] · Yasmin de Souza Lima Bitar[2] · José Admirço L. Filho[1] · Igor S. Schonhofen[1] · Edmundo J. N. Camara[2] · Leonardo Roever[3] · Hugo E. D. P. Cardoso[1] · Kevan M. Akrami[4]

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Abstract

Introduction Mechanical heart valves (MHV) are extremely durable, but they require permanent use of anticoagulation to prevent thromboembolic events. The only approved therapeutic options are vitamin K antagonists (VKAs), such as warfarin. As a drug class, clinical management is difficult, therefore new alternatives need to be evaluated.

Methods RIWA is a phase II/III, prospective, open-label, randomized, pilot study designed to investigate oral rivaroxaban 15 mg twice daily compared with dose-adjusted warfarin for the prevention of stroke (ischemic or hemorrhagic) and systemic embolism in patients with MHV, from August 2018 to December 2019. Patients will undergo transesophageal echocardiography at the beginning and the end of the study (follow-up time 90 days). On an explanatory basis, all events will be analyzed, including stroke, peripheral systemic embolism, valve thrombosis, significant bleeding and death.

Discussion Warfarin and similar VKAs are standard therapy for patients with an MHV. Even with the appropriate use of therapy, the incidence of thromboembolic events is high at 1–4% per year. Furthermore, bleeding risk is significant, ranging from 2 to 9% per year. The new frontier to be overcome in relation to use of the new oral anticoagulants is undoubtedly in patients with MHV. A significant portion of people with MHV worldwide will benefit if noninferiority of these new agents is confirmed.

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Key Points

Thromboembolic complications and anticoagulation-related bleeding are by far the most prevalent contributors to morbidity and mortality after surgery for mechanical heart valve (MHV).

The mainstay of treatment in guidelines remains indefinite anticoagulation with a vitamin K antagonist (VKA). The benefits of VKA therapy after MHV placement are marked.

Given the narrow therapeutic index, interactions, genetic variants, and need for blood monitoring of patients taking VKAs, it is necessary to evaluate new alternatives such as Factor Xa inhibitors.

✉ André R. Durães
andreduraes@gmail.com

[1] General Hospital Roberto Santos, Salvador, Bahia, Brazil

[2] Federal University of Bahia, Medical School-UFBA/FAMEB, XV de novembro Square, s/n-Largo do Terreiro de Jesus, Salvador, BA 40025-010, Brazil

[3] Federal University of Uberlândia, Uberlândia, Minas Gerais, Brazil

[4] Division of Infectious Disease, Department of Medicine, University of California, San Diego, San Diego, CA, USA

1 Introduction

For patients with severe and symptomatic valvular heart disease (VHD), valve replacement surgery improves morbidity and mortality outcomes. It is estimated that 4 million valve-replacement procedures have been performed over the last 50 years, and it remains the only definitive treatment for most patients with advanced VHD [1].

Patients who received mechanical heart valves (MHVs) have significantly lower mortality, higher cumulative incidence of bleeding and, in some age groups, stroke than recipients of a biologic prosthesis [2]. Despite this benefit, MHV demands lifelong anticoagulation with vitamin K antagonists (VKAs), most commonly warfarin, because of the high thrombogenicity of the prosthesis.

Even with the appropriate use of therapy, there is a high incidence of thromboembolic events: 1–4% per year. Furthermore, bleeding risk is significant, ranging from 2 to 9% per year [3]. Given the narrow therapeutic index, interactions, genetic variants, and need for blood monitoring of patients taking VKAs, alternatives to warfarin have now been made available, specifically, inhibitors that directly target Factor IIa (dabigatran) or Xa (rivaroxaban, apixaban, edoxaban) [4].

The only randomized controlled trial using a novel oral anticoagulant (NOAC) in patients with MHV (RE-ALIGN trial) was stopped early because of the higher incidence of negative outcomes, including thromboembolic events and bleeding [5]. The RE-ALIGN investigators proposed several reasons for the poor outcomes associated with dabigatran, including inadequate plasma levels of the drug and mechanisms of action. Although the results were disappointing, the trial was subject to several limitations. We recently published a series of cases with patients with MHV who had used rivaroxaban for 3 months without clinical complications [6]. Based on this, we believe the search for new antithrombotic alternatives in this scenario must continue.

The aim of the current study is to compare the incidence of thromboembolic events (stroke, systemic embolism, valvular thrombosis) and bleeding (intracerebral bleeding, digestive bleeding) in patients with MHV using rivaroxaban versus warfarin.

2 Methods

2.1 Study Objectives

The RIWA study (ClinicalTrials.gov NCT03566303) is a randomized, open-label, event-driven, pilot study designed to assess the incidence of thromboembolic (stroke, systemic embolic events, thrombosis of valve prosthesis—indicating efficacy) and bleeding (hemorrhagic stroke, gastrointestinal bleeding—indicating safety) events with the rivaroxaban-based strategy in comparison with those with the guideline-recommended warfarin dose-adjusted strategy after MHV replacement (with ≥ 3 months postoperatively). Although there is no predetermined specific outcome because it is an explanatory study, the incidence of ischemic stroke, peripheral embolic events, thrombosis of valve prosthesis, and major bleeding will be compared in both groups. The inclusion and exclusion criteria are outlined in Tables 1 and 2.

2.2 Study Population, Randomization and Follow-Up

From September 2018 to December 2019, patients with MHV ($n = 50$) aged between 18 and 75 years who are at least 3 months postoperative, in accordance with the eligibility criteria, will be recruited in the General Hospital Roberto Santos in Salvador-Brazil. A total of 100 subjects who provide informed consent will be randomized in a 1:1 ratio to 15 mg rivaroxaban twice daily or dose-adjusted warfarin. Figure 1 shows the study flow. Randomization will be performed using a random number table generated by a computerized electronic system. Patients randomized to an even number will be allocated to the rivaroxaban group, and those with an odd number will receive warfarin. Sealed, opaque and sequentially numbered envelopes containing the treatment allocation will be opened by the recruiting clinician on participant enrolment.

To participate in the study, subjects will undergo a computed tomography (CT) brain scan (without contrast) and a transesophageal echocardiogram (TEE) with the aim of increasing accuracy in the detection of subclinical events such as cerebral micro-infarcts or asymptomatic valve thrombosis. After 90 days of follow-up, even without events

Table 1 RIWA study inclusion criteria

Age 18–74 years at entry
Patients with MHV in mitral and/or aortic position, for at least 3 months postoperatively
Brain CT scan without hemorrhage or findings of acute cerebral infarction on the last 2 days of screening
Exclusion of atrial thrombus or valve prosthesis thrombosis by TEE on the last 2 days of screening
Written, informed consent

CT computed tomography, *MHV* mechanical heart valves, *TEE* transesophageal echocardiogram

Table 2 RIWA study exclusion criteria

Previous hemorrhagic stroke
Ischemic stroke in the last 3 months
Severe renal impairment (CrCl rates < 30 ml/min)
Active liver disease (any etiology)
Concomitant use of any antiplatelet (aspirin, clopidogrel, prasugrel, ticagrelor, ticlopidine, etc.)
Increased risk of bleeding (congenital or acquired)
Uncontrolled SAH
Gastrointestinal hemorrhage within the past year
Anemia (Hb level < 10 g/dl) or thrombocytopenia (platelet count < 100 × 109/l)
Active infective endocarditis
Pregnant or lactating women

ASA acetylsalicylic acid, *CrCl* creatinine clearance, *Hb* hemoglobin, *SAH* systemic arterial hypertension

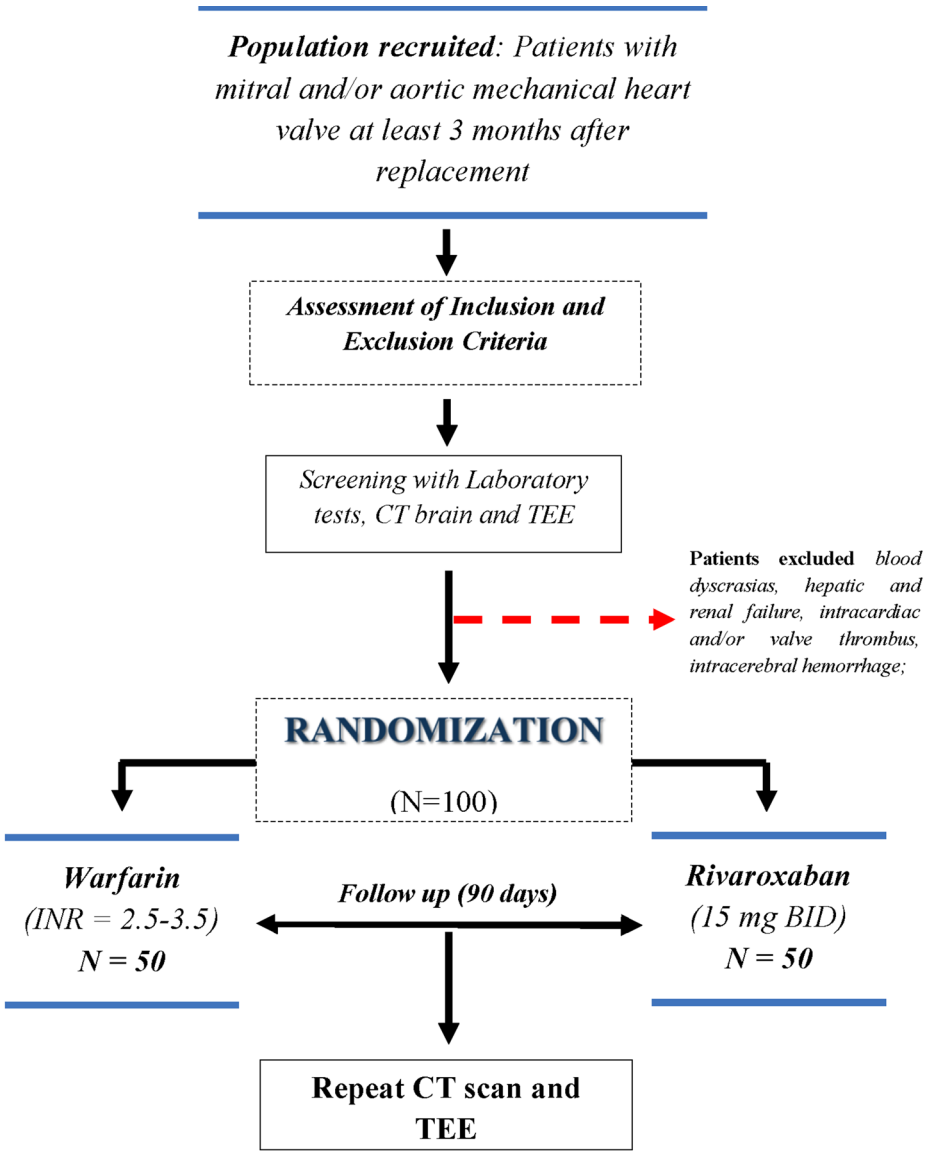

Fig. 1 RIWA study design. *ECG* electrocardiogram, *CT* computed tomography, *TEE* transesophageal echocardiography, *BID* twice daily

or symptoms, a repeat CT brain scan and TEE will be conducted. Transthoracic echocardiogram (TTE) will be performed at 30 and 60 days to check the gradient and mobility of the prostheses. On suspicion of valve thrombosis, the patient will be hospitalized and the TEE will be repeated. On-site visits are planned at days 30, 60, and 90. Telephone contact will be conducted weekly, and patients themselves will be able to contact the study at any time for clarification, questions and guidance.

2.3 Drug Administration Protocol

Rivaroxaban will be supplied as 15-mg tablets taken twice daily without international normalized ratio (INR) monitoring or food restriction. All patients randomized to rivaroxaban will continue to receive that drug for the duration of the study. After the end of follow-up, all subjects will return to warfarin use. Patients with previous use of warfarin will do washout with immediate introduction of rivaroxaban once the INR < 3.0.

Patients assigned to warfarin will require close coagulation monitoring to achieve the target INR (3.0, range 2.5–3.5 for mitral position, or 2.5, range 2.0–3.0 for isolated aortic position). Therefore, a protocol of monitoring and dosage adjustment for this drug is in place to ensure the safety and optimization of its use, as each patient may respond differently to the same dose. A warfarin dose-adjustment algorithm will be provided according to evidence-based guidelines [7, 8]. A modified Rosendaal et al. [9] method of linear interpolation will be used between each pair of measured INR values. For individuals with INR values outside the therapeutic range, INR will be repeated every 7 days for at least 3 months for improved time in therapeutic range accuracy [10]; only after this will they become candidates for study participation.

2.4 Definition of Outcome Events

Prosthetic valve thrombus is defined as soft and homogeneous, mobile or fixed echo density, similar to myocardium, located at the valve occluder, hinges, and/or valve struts. The largest diameter of the thrombus, as well as the length of the mobile portion, if present, will be measured. A diagnosis of pannus formation will be made when fixed, bright echo-dense structures, sometimes containing focal calcific deposits, are present primarily along the valve ring, with extension into the valve orifice [11]. In patients with inconclusive echocardiography, multidetector CT will be conducted to provide an accurate evaluation of the prosthetic valve structure and functional status [12].

Thromboembolic events involving the central nervous system are defined as a sudden, focal neurological deficit of presumed vascular origin lasting 24 h to 7 days (reversible ischemic neurological deficit) or enduring more than 7 days (stroke), confirmed by CT or magnetic resonance imaging and evaluated by a radiologist. Peripheral embolism will be diagnosed when there is sudden onset of arterial occlusion in the extremities (with or without cyanosis) and with reported absence of pulse, or sudden abdominal pain requiring urgent intervention (confirming acute intestinal ischemia during the surgical procedure).

The bleeding risk is based on the criteria of the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis [13] (Table 3). Minor bleeds are defined as clinical bleeds that do not fulfill the criteria for major bleeds.

2.5 Echocardiography

A standardized TTE and TEE examination, including the standard imaging planes, will be performed according to the recommendations of the American Society of Echocardiography [14]. Left ventricular ejection fraction will be calculated using the Simpson method, and the left atrial diameter will be measured in the M mode. Mitral valve E-wave peak velocity will also be measured and analyzed.

For TTE, a 1.7/3.4-MHz harmonic transducer will be used. TEE will be performed with a 6.7-MHz multiplane V5Ms transducer. The left atrium and its appendage will be closely inspected for the presence of spontaneous echo contrast (SEC) and thrombi by adjustment of the gain settings to optimal, to be able to distinguish SEC from electronic background noise. The degree of SEC will be categorized as being either absent (0), mild (1+), mild to moderate (2+), moderate (3+), or severe (4+) [15]. Prosthetic valve function and investigation of thrombus will follow the criteria of Zoghbi et al. [16].

2.6 Computed Tomography Brain Scan

Patients will routinely undergo only nonenhanced CT. The images may first be analyzed with a standard window width and level setting of approximately 40/20 HU, with a second narrower setting of 20/32 HU used to demonstrate subtle abnormalities that suggest ischemia. Perfusion CT and

Table 3 RIWA study major bleeding criteria

Fatal bleeding and/or
Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or
Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells

Adapted from Schulman et al. [13]

angiography will be used only in selected cases: if there is an acute stroke and if intracranial bleeding has been excluded in the first stage. The main expected change in suspected ischemic stroke is a cortical-subcortical hypoattenuating area within a vascular territory.

2.7 Safety Monitoring, Data Monitoring

The trial is externally monitored (ClinicalTrials Unit, Bern, Switzerland) in accordance with good clinical practice standards.

2.7.1 Monitoring Harm

All patients will have weekly follow-up by a dedicated and trained team to detect complications such as bleeding, poor adherence to therapy, embolic events or valve thrombosis. In addition, patients will routinely have face-to-face consultations every 30 days. Any event of valve thrombosis or embolism will be immediately reported to the ethics committee for consideration and decision about the suspension of the study.

2.8 Statistical Considerations

The primary efficacy and safety analyses will be conducted on the full analysis set of all randomized patients according to the intention-to-treat principle using endpoints and will be blindly adjudicated by an independent clinical event committee. SPSS 17.0 (SPSS Inc.; Chicago, IL, USA) will be used to perform statistical analysis of the collected data. Quantitative variables will be described as mean and standard deviation. The mean comparison will be performed using the Student's *t* test for independent populations or related populations, as appropriate. The qualitative and categorical variables will be presented as percentages, and their comparisons will be made with the Chi-squared or Fisher's exact test when indicated.

2.9 Use of Concomitant Drugs

The use of drugs such as acetylsalicylic acid, clopidogrel and other antiplatelet agents will not be allowed during the study period. The same applies to antiarrhythmic drugs that interact with rivaroxaban such as quinidine.

3 Discussion

Each year 300,000 prosthetic valves are replaced worldwide, of which 100,000 are in North America alone; this is projected to rise to 850,000 by the year 2050. In addition, cardiovascular diseases are responsible for 10–20% of all cardiac surgical procedures in the USA [1, 17].

The most plausible hypothesis for the failure of dabigatran (direct thrombin inhibitor) in prior studies is that clotting on MHV is triggered via activation of the contact system, resulting in the local generation of thrombin in concentrations that overwhelm those of dabigatran plasma levels [18]. This would be completely different with Factor Xa inhibitors, where one molecule of Factor Xa triggers the generation of 1000 molecules of thrombin, suggesting a greater theoretical effectiveness with inhibition of this level of the coagulation cascade [19]. Another hypothesis for the failure of dabigatran previously was use in patients with newly implanted valve prosthesis, where epithelization has not yet occurred [18].

On the other hand, in vitro MHV studies and animal models of rivaroxaban in terms of efficacy of thromboprophylaxis have shown promising results [20, 21]. As mentioned, our group's study was the first experience with rivaroxaban in MHV, and results were encouraging [6].

Compliance with Ethical Standards

Conflict of interest André R. Durães, MD, PhD, Yasmin de S. L. Bitar, Bachelor in Health, José Admirço L. Filho, MD, PhD, Igor S. Schonhofen, MD, Edmundo J. N. Camara, MD, PhD, Leonardo Roever, MD, MHS, Hugo E. D. P. Cardoso, and Kevan M. Akrami, MD have no conflicts of interest that are directly relevant to the content of this study.

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