Rivaroxaban in patients undergoing surgical mitral valve repair

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Rivaroxaban in patients undergoing surgical mitral valve repair

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Abstract

In patients undergoing mitral valve repair (MVre), a 3-month course of anticoagulation is currently recommended. The role of the non-vitamin K antagonist oral anticoagulants has here been scarcely studied. In the present mixed cohort study, the safety and efficacy of rivaroxaban (prospective analysis) were compared with those of warfarin (retrospective analysis) in patients undergoing MVre. Anticoagulation therapy was continued for at least 3 months, and the patients were followed for 1 year following surgery. The present study recruited 736 patients undergoing MVre with or without concomitant coronary artery bypass or surgical repair on the other valves. Concomitant valvular replacement and severe chronic kidney diseases were the most important exclusion criteria. The final analysis was conducted on 153 patients treated with rivaroxaban and 144 patients treated with warfarin. Dissimilarities in baseline characteristics necessitated propensity score matching, in which 104 patients in each group were compared. No major bleeding or cerebrovascular accident occurred during the 1-year follow-up. Clinically relevant non-major bleeding was reported in 2 patients in the rivaroxaban group and 4 patients in the warfarin group, a difference non-statistically significant before and after propensity score matching ($P=0.371$ and $P=0.407$, respectively). The type of anticoagulation did not predict the 1-year outcome (HR 2.165, 95% CI 0.376 to 12.460; $P=0.387$). In this mixed cohort study, rivaroxaban was both safe and efficient in patients with MVre. Such preliminary results should prompt larger randomized controlled trials.

Keywords Mitral valve repair · Antithrombotic regimen · Warfarin · Novel oral anticoagulation therapy · Rivaroxaban

Highlights

- Largest comparison between rivaroxaban vs. warfarin in patients undergoing MV repair.
- No major bleeding or cerebrovascular accident were observed in both groups.
- No significant difference between the 2 groups regarding CRNMB.
- Rivaroxaban appears to be a safe and efficient option in post-MV repair patients and needed to be approved in larger clinical trial.

Introduction

Mitral valve repair (MVre) is currently the procedure of choice among surgical solutions for primary mitral regurgitation [1]. The optimal post-MVre antithrombotic regimen is

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a matter of debate [2]. The increase in the thrombogenicity of annuloplasty rings and the risk of atrial fibrillation (AF) development in the early post-surgical period prompt the use of anticoagulation therapy for at least a short (usually 3 months) post-procedural time [3].

Initially introduced as anticoagulation therapy in patients with "non-valvular" AF, the non-vitamin K antagonist oral anticoagulants (NOACs) have been used more and more in recent years, and also in patients with various forms of valvular heart disease [4]. Considerably large numbers of patients with different types of valvular heart disease have been included in the pivotal randomized controlled trials testing different NOACs [4–8]. However, the number of patients undergoing MVre has been very limited in all those trials, as well as in some large-scale registries [4–9].

In a mixed cohort study, we here report on the safety and efficiency of one NOAC, rivaroxaban, in such patients. We compared the results of prospectively recruited patients with MVre treated with rivaroxaban with those of a propensity-matched previously recruited group of patients undergoing MVre, but treated with warfarin recruited in our hospital.

Methods

Study population

This is a mixed cohort study performed on patients candidate to MVre for whom either warfarin or rivaroxaban were administered as the sole anticoagulation therapy. Data on the rivaroxaban group were collected prospectively. For a comparative propensity-matched analysis, we collected information from our database regarding patients candidate to MVre, but treated with warfarin. The study protocol was approved by the Ethics Committee of the Rajaie Cardiovascular, Medical and Research Center (Tehran, Iran). All prospectively recruited patients signed a written informed consent before participation. For the analyses on retrospectively collected data on patients treated with warfarin, we obtained oral informed consent during telephone follow-up interviews.

The present study included all patients aged at least 18 years with mitral regurgitation candidate to MVre at the Rajaie Cardiovascular, Medical and Research Center from October 2010 to April 2019. The recruitment of the prospective cohort treating patients with rivaroxaban started in November 2016. Of note, patients with concomitant aortic, tricuspid, and pulmonary valve repair or coronary artery bypass graft surgery were included in the present study. The study flowchart and the excluded patients are presented in Fig. 1.

Anticoagulation regimen

Anticoagulation therapy was started on the second day after surgery. Rivaroxaban 20 mg/once daily was administered in patients with an estimated creatinine clearance (CrCl, Cockroft-Gault formula) of 50 mL/min or higher;

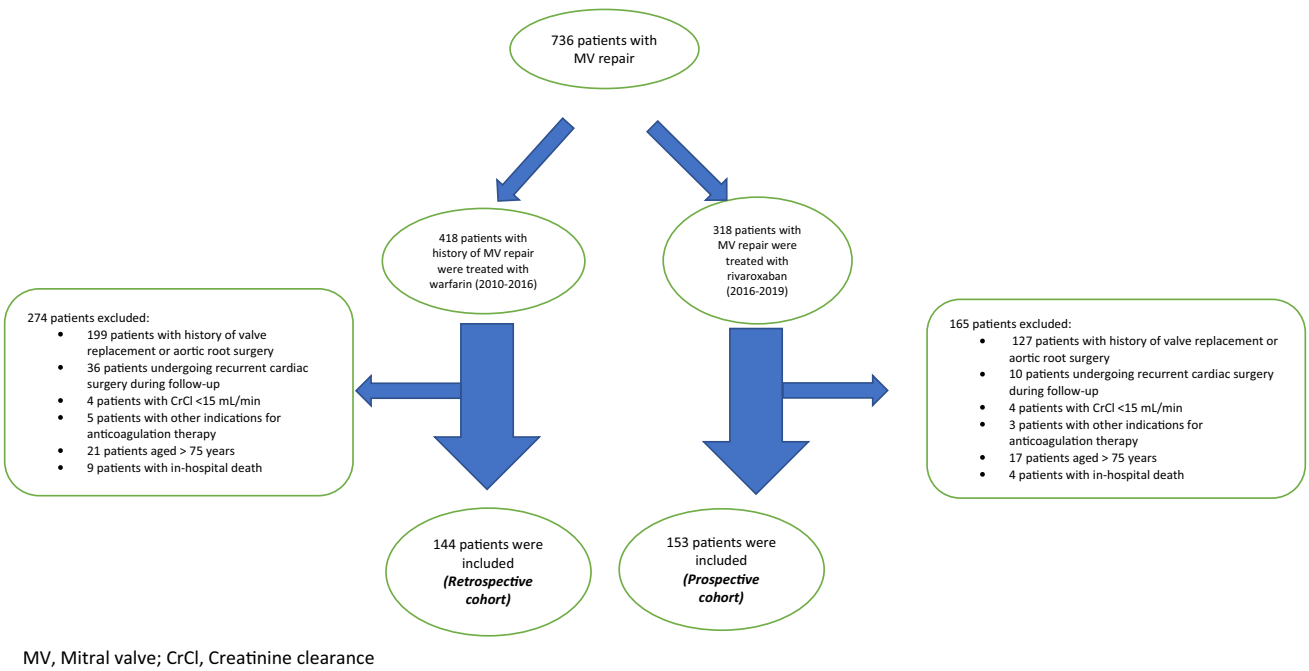

Fig. 1 Prospective and retrospective cohort flowchart. *MV* mitral valve, *CrCl* creatinine clearance

rivaroxaban 15 mg once daily was administered in patients with CrCl between 15 and 49 mL/min [2]. Patients treated with warfarin were kept with an international normalized ratio (INR) of 2 to 3 was considered. Parenteral anticoagulation with a low-molecular weight heparin (enoxaparin 1 mg/kg twice a day) was administered until therapeutic INR was achieved. Patients were discharged only after a reliable INR had been reached. For all patients, anticoagulation therapy was continued at least for 3 months after surgery. In patients with a history of AF before MVre or during the 3-month follow-up period, anticoagulation was continued indefinitely. For the other patients, aspirin 80 mg daily was then continued indefinitely.

Patients follow up

All the patients were followed-up for 1 year after the surgical procedure. Patients undergoing valvular heat surgery have a predefined protocol for the follow-up. Clinic visits are scheduled in the first, third, sixth and 12-month after surgery. Also echocardiography exams were routinely performed on the first and sixth months after surgery. Patients treated with warfarin, have received monthly care from our warfarin clinic after the INR were stabilized into therapeutic range.

Study outcomes

Our primary outcome was the occurrence of major or clinically relevant non-major bleeding according to the classification of the International Society on Thrombosis and Haemostasis (ISTH) [10]. Ischemic stroke or transient ischemic attack was considered the secondary outcome. All such outcomes were evaluated for 1 year after MVre.

Statistical analysis was presented in the supplement.

Results

After the implementation of the inclusion and exclusion criteria, 153 and 144 patients were included in the prospective and retrospective analyses, respectively (Fig. 1). Demographic, clinical, and procedural characteristics of the two groups are summarized in Table 1, showing that clinical characteristics were statistically similar, with the exception of diabetes mellitus, hypertension, chronic kidney disease, left ventricular function and concomitant coronary artery bypass graft surgery. Anticoagulation was discontinued after 3 months in 129 (89.3%) patients in the rivaroxaban group and 119 (82.6%) patients in the warfarin group.

There was no case of major bleeding in either group during the 1-year follow-up. Six cases of clinically relevant

Table 1 Baseline characteristics and outcomes in the study groups

	Before propensity score matching			After propensity score matching		
	Rivaroxaban (n = 153)	Warfarin (n = 144)	*P*-value	Rivaroxaban (n = 104)	Warfarin (n = 104)	*P*-value
Age, year	49.9 ± 15	51.9 ± 14.3	0.247	50.3 ± 12.9	49.6 ± 15.3	0.732
Male gender	60 (39.5%)	51 (35.4%)	0.471	42 (40.4%)	42 (40.4%)	1
Prior histories						
Hypertension	35 (22.9%	58 (40.3%)	0.001	25 (24%)	21 (20.2%)	0.504
Diabetes mellitus	7 (4.9%)	34 (22.2%)	< 0.001	9 (8.7%)	7 (5%)	0.603
CKD	3 (2.1%)	13 (8.5%)	0.014	4 (3.8%)	3 (2.9%)	0.701
Hyperlipidemia	25 (16.3%)	31 (21.5%)	0.253	19 (18.3%)	17 (16.3%)	0.714
Perioperative features						
LVEF	44.01 ± 10.4	46.66 ± 9.2	0.022	45.5 ± 9.6	46.1 ± 9.3	0.636
AF rhythm	24 (15.7%)	25 (17.4%)	0.698	15 (14.4%)	18 (17.3%)	0.569
HAS-BLED ≥ 3	28 (18.3%)	20 (13.9%)	0.302	11 (10.6%)	17 (16.3%)	0.223
Concomitant surgeries						
Valvular repair	24 (15.7%)	20 (13.9%)	0.663	14 (13.5%)	14 (13.5%)	1
CABG	52 (34%)	29 (20.3%)	0.008	27 (26%)	23 (22.1%)	0.516
Events at follow-up						
CRNMB	2 (1.4%)	4 (2.6%)	0.371	2 (1.9%)	4 (3.8%)	0.407
Major bleeding	0	0		0	0	
TIA/CVA	0	0		0	0	

All variables are expressed as number (percentage) or mean ± SD

CABG coronary artery bypass graft surgery, *CKD* chronic kidney disease, *CRNMB* clinically relevant non-major bleeding, *CVA* cerebrovascular events, *LVEF* left ventricular ejection fraction, *MV* mitral valve

non-major bleeding were observed overall: 2 cases of rectorrhagia in each group and 2 cases of vaginal bleeding in the warfarin group (Table 1). There were no statistically significant differences between the 2 groups regarding bleeding events.

There were no cases of cerebrovascular accident/transient ischemic attack in the two groups.

Dissimilarities in the baseline characteristics of our study groups prompted us to perform a propensity-matched score analysis (Table 1). After matching, 104 patients from each group were introduced into the new analysis, which once again revealed no significant differences between the 2 groups as to bleeding adverse events. For clinically relevant non-major bleeding, the average treatment effect was 0.002 ± 0.027 ($t = 0.063$, $P > 0.05$).

There were clearly no differences between the groups in time-dependent analyses, as shown by Kaplan–Meier curves (Supplement Fig. 1). In Cox regression analysis, the type of anticoagulation failed to predict the 1-year outcome (HR 2.165, 95% CI 0.376 to 12.460; $P = 0.387$) (Supplement Table 1).

Discussion

This study shows the viability of the practical once-daily dosing with the NOAC rivaroxaban in the early time period (3 months) following MVre in the largest cohort of such patients ever reported.

The optimal anticoagulation therapy for those patients is a matter of debate and based on a low level of evidence [2]. Thrombogenicity of the annuloplasty rings and the risk of developing AF in the early post-surgical period justify the need for early anticoagulation in patients undergoing MVre, and for these reasons guidelines suggest a course of 3 month anticoagulation with a vitamin K antagonist [2, 11]. This is the dominant approach among surgeons: Vaughan et al. reported that 64% of surgeons in the United Kingdom recommended warfarin as the early antithrombotic regimen for patients undergoing MVre [12]. Valeur et al., in their analysis on 2188 patients undergoing MVre from the Danish national registry, showed that warfarin carried a lower risk of death/stroke at 3 months (HR 0.28, 95% CI 0.13 to 0.62; $P = 0.002$) compared with a non-warfarin regimen, with no significant differences in bleeding complications [13].

Although the initial indication for NOACs was "non-valvular AF", major randomized controlled trials have included considerably large numbers of patients with valvular heart diseases in their final analysis [8]. Two of these investigations—namely the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial [5] and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [6]—specifically included patients undergoing bioprosthetic valvular replacement or valvular repair, and reported that the tested NOACs (edoxaban and apixaban, respectively) were safe and effective in this group of patients. Russo et al., in their multicenter report on the role of NOACs in patients with bioprosthetic heart valves/prior surgical valve repair, showed an acceptable annual incidence rate of thromboembolism (0.8%) and major bleeding (1.3%) [14]. Importantly, however, in all such investigations the number of the MVre patients was limited to < 50 patients. In the present study, 153 MVre patients were treated with rivaroxaban for at least 3 months and followed for 1 year. No cerebrovascular accident/transient ischemic attack or major bleeding was observed. Two cases of clinically relevant non-major bleeding (rectorrhagia) were detected. These incidences are comparable to those reported by the ENGAGE AF-TIMI 48 trial [5], the ARISTOTLE trial [6], and a study by Russo et al. [6]. No significant differences were detected with patients on warfarin as to safety or efficacy events in our retrospective analysis.

Study limitation (see the supplement)

In conclusion, rivaroxaban appears to have acceptable safety and efficacy profiles in patients undergoing MVre. Despite our study limitations, and in the foreseeable absence of forthcoming randomized controlled trials, we consider this report important for the expansion of the practical use of this NOACs—and, in the light of the overall literature, probably of all factor Xa inhibitors—in this setting. Certainly, further large scale randomized controlled trials are needed to determine the role of NOAC in MVre patients.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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