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ORIGINAL ARTICLE

Rivaroxaban in patients with mechanical heart valves: a pilot study

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Abstract

Background

Patients with mechanical heart valves are still not eligible for treatment with direct oral anticoagulants (DOAC). We aimed to conduct a proof-of-principle study investigating the anti-Xa inhibitor rivaroxaban as antithrombotic treatment in patients with recent mechanical aortic valve replacement.

Materials and Methods

Low-risk patients scheduled for elective mechanical aortic valve replacement were treated with rivaroxaban 20 mg once daily (OD) in a prospective cohort study, started on day 3 postoperatively and given for 6 months. The study was registered at ClinicalTrials.gov (#NCT02128841).

Results

Ten patients were included (median age, 48; range range 39 to 60). Indication was aortic valve stenosis in 6 patients, aortic root aneurysm with severe aortic valve regurgitation in 3 patients, and mixed stenosis/regurgitation in 1 patient. Neither thromboembolic nor bleeding events were observed, and no patient died. Absence of valve thrombosis was demonstrated in all patients. On day 7, median D-dimers were 2723 µg/L (inter-quartile range [IQR] 2281, 369 µg/L), median TAT levels were 4.5 µg/L (IQR 4.1, 5.6 µg/L); and median peak thrombin generation was 150 nM (IQR 91, 183). On day 90, median D-dimers were 426 µg/L (IQR 278, 569), median TAT levels were 2.7 µg/L (IQR 2.2, 3.1), and median peak thrombin generation were 66 nM (IQR 62, 87).

Conclusions

Rivaroxaban 20 mg OD was safe and effective in a pilot study of 10 low risk patients with mechanical aortic heart valve. Our results justify larger studies investigating the application of anti-Xa inhibitors in patients with mechanical heart valves.

Keywords

- rivaroxaban/therapeutic use
- heart valve prosthesis
- thromboembolism
- blood coagulation/drug effects

Essentials

- Direct oral anticoagulants are still not applicable to patients with mechanical heart valves
- We conducted a proof-of-principle pilot study using rivaroxaban 20 mg OD in 10 patients
- Rivaroxaban was safe and effective in low risk patients with mechanical aortic heart valve
- Our results justify larger studies in this population

Introduction

Implanting a mechanical heart valve exposes patient at a high risk for thromboembolic events. [1, 2] Complications like valvular thrombosis with obstruction of outflow or major stroke might result in lifelong disability or even death. [3] Thus, all patients with mechanical heart valves require lifelong anticoagulant therapy. [4-6] Treatment with vitamin K antagonists (VKA) demonstrated to be highly effective, with the downside of a relevant bleeding risk however. [7] Treatment with VKA is started as soon as possible after operation, mostly following a bridging period with unfractionated heparin (UFH) and/or low molecular weight heparins. [4-6] In clinical practice, treatment with VKA is however associated with a number of important drawbacks. The onset is slow, requiring close medical care and bridging at start or in perioperative situations. [8] VKA interact with food and drugs leading to a changing anticoagulant intensity. [8] Polymorphisms of cytochrome P450 enzyme gene *(CYP2C9)* and vitamin K epoxide reductase *(VKORC1)* result in a large variability among individuals. [9] Thus, a close laboratory monitoring of VKA is required, which is costly and inconvenient for the patient. [10] Nevertheless, a high quality of anticoagulation can be achieved in special treatment schemes, such as patient self-management. [11-13]

Direct oral anticoagulants (DOAC) have replaced VKA in several clinical situations because of the favorable risk-benefit profile and practicability issues. DOAC can be administered in fixed doses without the need of routine laboratory monitoring, the potential for interactions with food and drugs is much lower compared to VKA, and the risk of intracranial hemorrhages – which is regarded as the most severe bleeding complication – is markedly lower compared to VKA. [14-18] It is however uncertain whether the benefits and advantages of DOAC observed in patients with atrial fibrillation and venous thromboembolism can be expected in patients with mechanical heart valves as well. [19] A number of in-vitro and animal studies suggested that DOAC are able to prevent clotting of mechanical heart valves. [20-24] In addition, case reports are available reporting successful treatment of valve thrombosis with the use of DOAC. [25, 26] In a randomized controlled trial comparing warfarin with the direct oral thrombin-inhibitor dabigatran for the prevention of thromboembolic events in patients with mechanical heart valves, the treatment with dabigatran was associated with an increased risk of thromboembolic and bleeding events however. [27] To date, it remains unclear whether anti-Xa inhibitors such as

rivaroxaban may replace VKA for the prevention of thromboembolism in patients with mechanical heart valves. A pilot study in a limited number of patients can provide important insights for the planning of a large clinical trial.

With the present pilot study, we aimed to explore the feasibility and the safety of rivaroxaban treatment for prevention of thromboembolic complications in patients with low-risk mechanical heart valves and providing important information for planning larger clinical studies.

Material and Methods

Study design

This is a prospective, open-label pilot studying the feasibility of a large-scale randomized controlled trial to be conducted in patients with AVR. No control group was included. The steering board of the study decided to limit the exposure time of rivaroxaban to 6 months because of the unclear benefit-to-risk profile in this setting. All patients signed informed consent. The protocol was approved by the appropriate ethical committee (Kantonale Ethikkommission Bern; #154/10) and by the Swiss Agency for Therapeutic Products (Swissmedic; #2011DR2223). It was registered at ClinicalTrials.gov (#NCT02128841). The study has been conducted in accordance with the Declaration of Helsinki. The study was terminated after 10 patients treated because no outcomes were observed, practicability considerations and low recruitment.

Setting and participants

The study was conducted at Inselspital, the Hospital of the University in Bern, a tertiary hospital in Switzerland with a large cardiac surgery department. Patients with aortic valve disease requiring a valve replacement and qualifying for a mechanical prosthesis were eligible. Inclusion criteria were (a) patients requiring a mechanical aortic valve replacement including combined procedures (e.g. coronary artery bypass, composite graft, aortic valve replacement, and aortic root enlargement), (b) no mechanical ventilation three days after surgery, (c) age between 18 and 70 years, (d) preserved left ventricular ejection fraction (≥30%) preoperatively, and (e) written informed consent. Patients were excluded in case of atrial fibrillation (rivaroxaban was not licensed in Switzerland for patients with atrial fibrillation at the time the protocol was drafted). The complete list of exclusion criteria can be found in the supplementary material (original study protocol). Medtronic open Pivot© prostheses were used.

Intervention

Eligibility of patients was checked, and patients included one day prior to surgery. In case of newly developed atrial fibrillation, patients were excluded postoperatively. Unfractionated heparin was stopped on day 3 postoperatively, and rivaroxaban 20 mg once daily (OD) was started two hours later. Rivaroxaban was administered once daily in the evening with supper and vitamin K antagonists (VKA) were withhold. Treatment was continued for 6 months and patients were then switched to VKA for the long-term treatment (Phenprocoumon). Compliance was checked by collecting drug blister packs and unused tablets at follow-up visits. The dosage of 20 mg OD was chosen being the most intensive dosage in available phase III studies in patients with atrial fibrillation and venous thromboembolism. [28, 29]

Primary and secondary outcome measures

In the original study protocol, the primary outcome was defined as a composite of major thromboembolic or bleeding event as well as death (prosthetic thrombus requiring reoperation/ intervention, major bleeding, visceral ischemia, stroke, pulmonary embolism, myocardial infarction, or death). Secondary outcomes were the above-mentioned adverse events individually. D-dimers, thrombin-antithrombin complex (TAT), as well as thrombin generation were additionally observed as markers of coagulation activation and potential, respectively.

Follow-up procedures

Follow-up was conducted daily until discharge, and at day 30, day 90, as well as day 180 postoperatively. A flow chart illustrating the study procedures is shown in Figure 1. A thorough clinical and neurological investigation was conducted to specifically recognize thromboembolic events. D-dimers, TAT complexes, as well as thrombin generation were determined. An echocardiography as well as transcranial doppler investigation was conducted at discharge and at day 90 and 180. Patients were referred to intermediate GP visits according to clinical practice. GPs were instructed to look for signs and symptoms regarding thromboembolic complications. Switching from Rivaroxaban to VKA at the end of the study at 6 months was done by the GP.

Statistical analysis

As a pilot study, the number of patients was mainly based on practical considerations and 30 patients were deemed to be feasibly by the scientific board. The study was however terminated

after 10 patients treated because no adverse events were observed, but also because of practicability considerations and low recruitment. Patient characteristics and outcomes were reported as numbers (percent) or median (range) as appropriate. Distribution of D-dimers, TAT complexes, as well as thrombin generation over time were shown as median and range (Figure 2). The Stata 14.2 statistics software package was used (StataCorp. 2014. Stata Statistical Software: Release 14 College Station, TX: StataCorp LP). Figure 2 was created using Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

Patient characteristics and intervention

Ten patients were included between 1st of September 2013 and 31st of December 2014; two additional patients were excluded postoperatively because of atrial fibrillation (according to the protocol). The flow of the patients is shown in Figure 1, detailed patient characteristics are reported in Table 1. The median age was 48 years (range 39 to 60), 9 patients were male (90%). Extent of heart failure was New York Heart Association Functional Classification (NYHA) I in 5 patients (50%), and NYHA II in 5 patients (50%). Coronary heart disease was absent in all patients; no concomitant disorders were present in the majority of patients. Indication for aortic valve replacement was aortic valve stenosis in 5 patients (50%) and mixed aortic valve disease or combined with thoracic aortic disorders in all other patients. Isolated aortic valve replacement was done in 6 patients (60%) and concomitant thoracic aortic procedures in 4 patients (40%). Compliance with rivaroxaban OD was adequate in all patients according to drug blister packs returned.

Clinical outcomes and imaging results

Physical and neurological examination until discharge did not indicate any thromboembolic event. Echocardiography performed before discharge and at days 90 and 180 did neither demonstrate thrombotic material nor valve dysfunction (Table 2). Results of transcranial doppler sonography were normal (done in a random sample of 3 patients). At the follow-up visits on day 90 and day 180, the physical and neurological investigation did not indicate any thromboembolic event as well. No significant bleedings were observed, neither major nor minor or clinically relevant non-major bleedings.

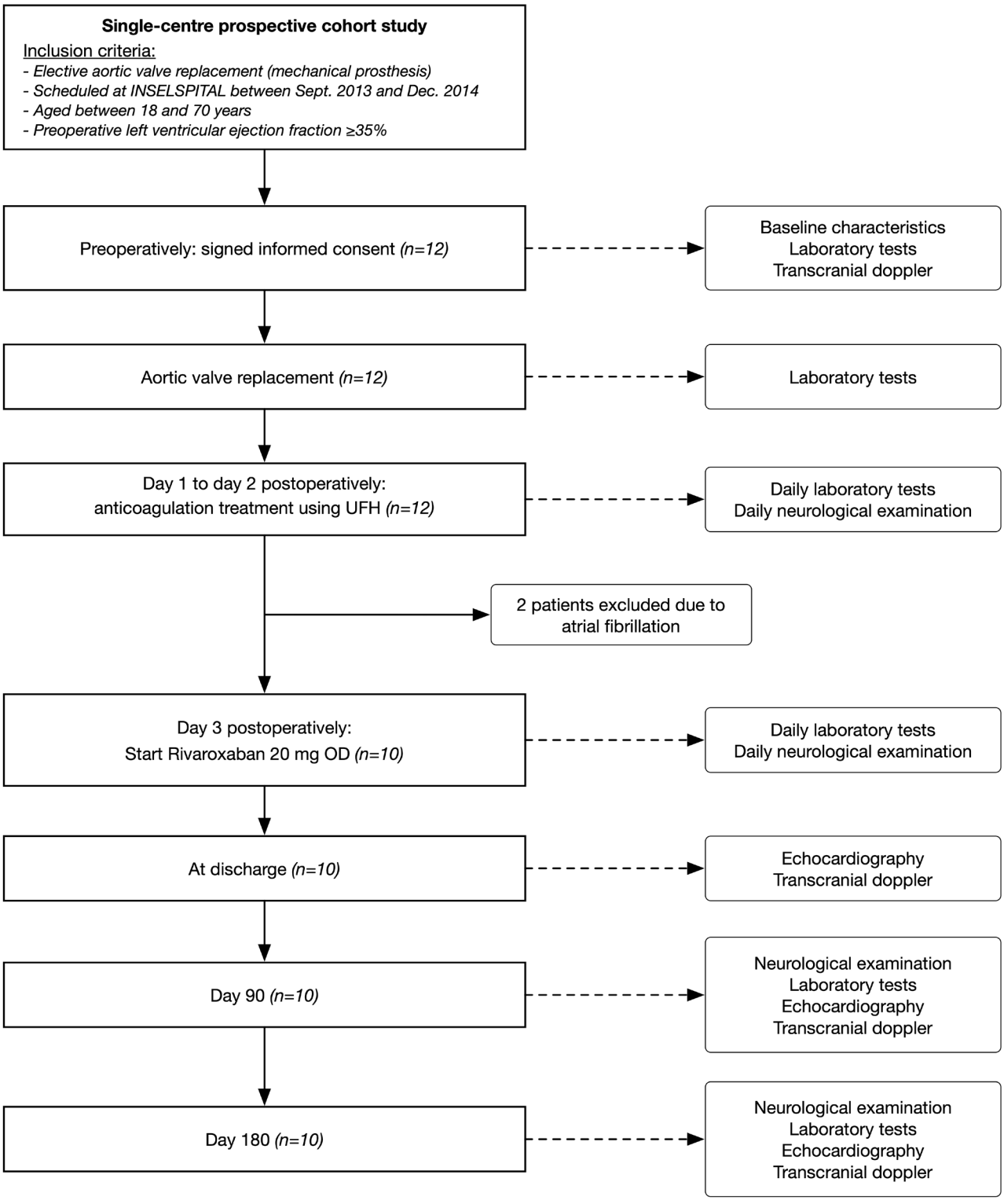

Figure 1: Flow of the patients and study procedures; Abbreviations: OD, once daily

Patient	Age *(years)*	Sex	BMI *(kg/m²)*	Indication for AVR	Extend of heart failure	Type of intervention	Type of valve+ *(mm)*	Concomitant disorders
1	47	Male	28	Aortic valve stenosis	NYHA I	Isolated AVR	20	None
2	60	Male	35	Aortic valve stenosis	NYHA II	Isolated AVR	24	None
3	51	Male	31	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
4	50	Male	25	Aortic stenosis and regurgitation; aortic root aneurysm	NYHA I	Root replacement	25	None
5	49	Male	26	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
6	48	Male	24	Aortic valve stenosis	NYHA II	Isolated AVR	22	None
7	39	Male	29	Aortic valve insufficiency	NYHA II	Isolated AVR	24	None
8	48	Male	30	Aortic root aneurysm	NYHA I	Root replacement	23	Dyslipidemia
9	44	Female	24	Aortic stenosis and regurgitation	NYHA I	AVR, replacement of ascending aorta and aortic arch	22	None
10	48	Male	26	Aortic root aneurysm	NYHA I	Root replacement	25	History of thyroid cancer

Table 1: Patient characteristics * *AVR, aortic valve replacement; + Medtronic open Pivot©; Abbreviations: BMI, body mass index; NYHA, New York Heart Association Functional Classification*

Patient	LVEF * (%)	Size of valve (mm)	Mean gradient (mmHg)	Peak gradient (mmHg)	Thrombus formation+	Movement of valve+
1	65	20	12	25	None	Normal
2	65	24	16	29	None	Normal
3	65	22	19	39	None	Normal
4	65	25	8	17	None	Normal
5	60	22	10	20	None	Normal
6	60	22	13	21	None	Normal
7	40	24	9	16	None	Normal
8	55	23	18	42	None	Normal
9	60	22	14	25	None	Normal
10	50	25	12	17	None	Normal

Table 2: Echocardiography results at discharge * *Left ventricular ejection fraction (%); +assessed on day 90 and day 180 as well*

Laboratory outcomes

The course of D-dimer, TAT as well as thrombin generation pre- and postoperatively is shown in Figure 2. Preoperatively, median D-dimer result was 198 µg/L (range 114, 1284) and increased postoperatively to a maximum level of 2723 µg/L (day 7; range 1672, 5695). At day 90, D-dimer level decreased to 60 µg/L (range 35, 217). Median TAT complexes increased from 2.8 µg/L prior to surgery (range 1.8, 15) to 4.9 µg/L at day 5 (3.5, 10), and decreased to 2.7 µg/L at day 90 (1.0, 4.3). Peak thrombin generation was 157 nM preoperatively (range 109, 339), 205 nM at day 4 (166, 276), and 66 nM at day 90 (17, 95).

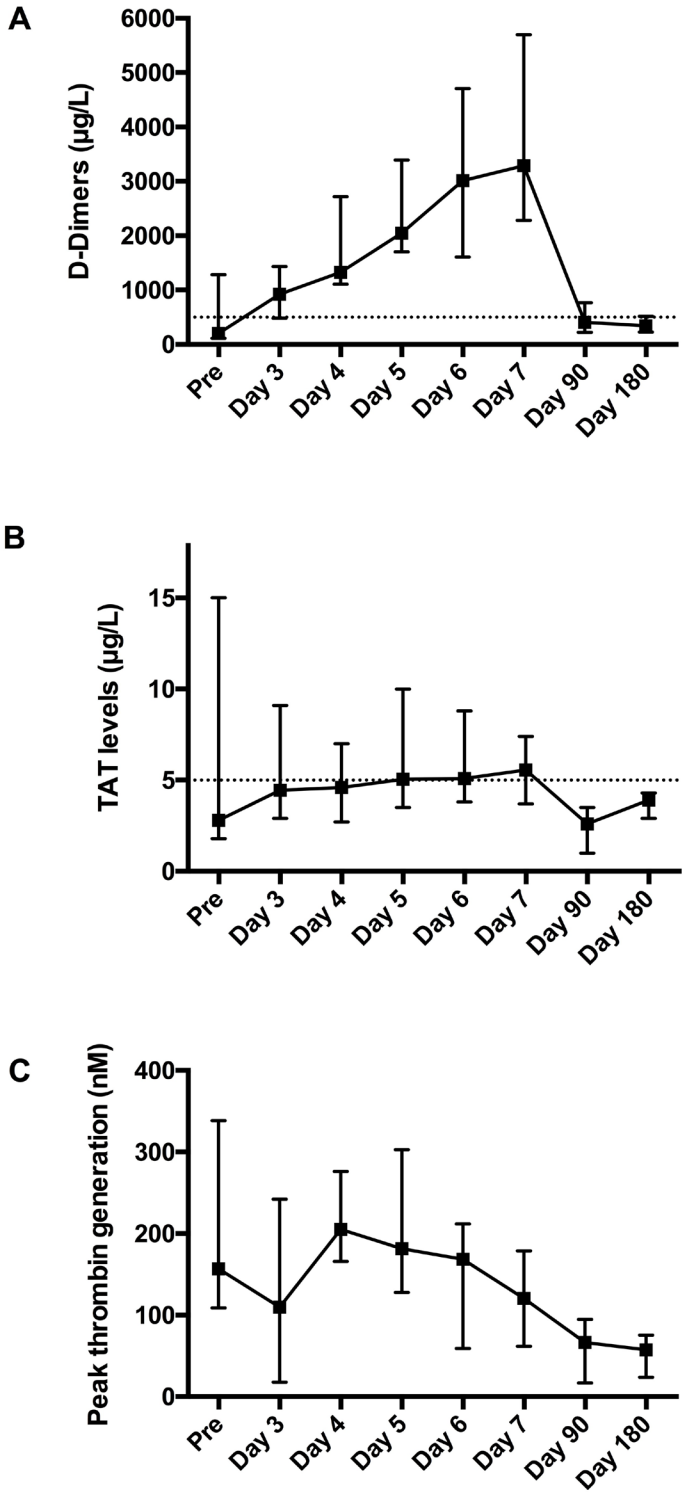

Figure 2: Course of D-dimer, thrombin-antithrombin complex, as well as peak thrombin generation in 10 patients treated with rivaroxaban 20 mg once daily after aortic valve replacement

Discussion

Rivaroxaban treatment was safe, efficient and feasible for prevention of thromboembolic events in low-risk patients who received a mechanical aortic heart valve. Neither thromboembolic nor bleeding events were observed during the observation period of 6 months. Laboratory parameters of thrombin generation and coagulation activation suggest adequate response to anticoagulation treatment. However, recruitment was sluggish and study was terminated early.

This is the first study prospectively exploring the safety and efficacy of rivaroxaban initiated after mechanical valve placement. Our results are in-line with few cases reporting the successful treatment of a valve thrombosis using rivaroxaban. [25, 26] In another study, thromboembolism could be prevented in 7 patients with isolated mitral valve replacement observed for 3 months. [30] Our results are however in contrast to a randomized controlled trial with dabigatran that was conducted in patients with mechanical heart valve (n=252). [27] Several explanations may explain this difference. First and most important, the pharmacological mechanism of action of rivaroxaban (direct factor Xa inhibitor) is different from dabigatran (direct thrombin inhibitor) and this may result in a different efficacy profile in presence of artificial surfaces. [19]. Second, the study by Eikelboom observed a vast variety of patients including aortic and mitral valve prosthesis as well as patients operated within the past 7 days and those who had undergone such replacement at least 3 months earlier. Third, the compliance with rivaroxaban, being the intake just once a day, might be higher as with dabigatran were the dosage is distributed twice a day. And fourth, the number of patients in our study was too low to detect adverse events. This is the major limitation of our work and the question arises why the enrollment was lower than expected. At the time of patient recruitment, practical knowledge on DOAC was still relatively limited and many patients in Switzerland attended the training for patient self-management of VKA which is well-recognised as a high-quality treatment scheme [11, 13]. In addition, physicians also hesitated to propose DOAC treatment because of the recent publication of the unfavorable results obtained with dabigatran [27].

The strength of our investigation is the fact of being a prospective cohort study where procedures and follow-up were defined strictly in advance. Assessment of potential thromboembolic events was done very thoroughly, ensuring valid results. In addition, we studied a comprehensive set of clinical outcomes as well as laboratory measures describing activation of coagulation. Important

limitations are the lack of a control group, a restricted exposure time and the very low number of patients. In addition, no information is available on the anticoagulation treatment after 6 months. Thus, the results obtained shall be interpreted with caution. In particular, considering the clear results obtained by Eikelboom and colleagues [27] and the very limited methodology of our study, it remains current standard not to use DOAC in patients with mechanical heart valves.

Nevertheless, our results – in-line with existing case reports – suggest that a large randomized clinical trial studying rivaroxaban in patients with mechanical heart valve is feasible and urgently needed. The number of thromboembolic and bleeding events was low, facilitating a future non-inferiority trial. However, the screening and inclusion of patients must be planned carefully in a multicenter design to ensure an adequate inclusion rate.

Conclusions

Rivaroxaban treatment (20 mg OD) to prevent thromboembolic events in low-risk patients receiving a mechanical aortic heart valve patients is feasible. The results of this small pilot trial are very promising since no thromboembolic nor bleeding events were observed within six months. Laboratory parameters suggest adequate response to anticoagulation treatment. Our results justify large randomized controlled trials investigating the treatment of rivaroxaban anti-Xa inhibitors in patients with mechanical heart valves.

Author contributtions

AW, LA, and TC designed the study and developed the study protocol. AW, ER, and LA collected the data. MN and ER analyzed the data and wrote the manuscript. TC, DR and LE reviewed the analysis and the manuscript. TC and LA provided infrastructure. All authors intellectually reviewed and approved the manuscript.

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Disclosures of Conflict of Interests

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