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# Impact of aspirin use in the incidence of thromboembolic events after bioprosthesis replacement in patients with rheumatic disease

*Impacto da aspirina na incidência de eventos tromboembólicos após implante de bioprótese valvar cardíaca na doença reumática crônica*

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## Abstract

**Introduction:** There is still much debate regarding the kind of antithrombotic therapy in the immediate postoperative period of bioprosthesis replacement (first three months). Thus, the authors consider relevant to determine the contemporary incidence of thromboembolic events in rheumatic patients early after implantation of aortic and mitral bioprosthesis replacement (first 90 days in the post-operative period) and perform a comparison between isolated Aspirin uses *versus* no-antiplatelet therapy, in this same context.

**Methods:** Between the period of January 2010 to July 2012, all consecutive rheumatic patients, with basal sinus rhythm, who performed mitral and aortic valve replacement with bioprosthesis (pericardial bovine), were included in this prospective cohort study, 184 patients in total. The primary endpoint evaluated were the rate of embolic events.

**Results:** In the first 30 days, there were three cerebral ischemic events among patients treated in Aspirin group (5.2%) compared with two events in patients without Aspirin therapy (1.7%), HR = 3.18; 95% CI 0.5 to 19.6;  $P=0.33$ . Between 31 and 90 days postoperatively, no patient had a primary outcome. The embolism-free survival, bleeding events and the overall survival

were not statistically significant between the aspirin and no-antiplatelet groups.

**Conclusion:** In conclusion, in this prospective cohort of rheumatic patients, we found a low and very rare incidence rate of embolic events during the first 90 days postoperative period in mitral and isolated aortic position, respectively. The use of aspirin did not significantly reduce the rate of thromboembolism.

**Descriptors:** Aspirin. Stroke. Bioprosthesis. Rheumatic heart disease.

## Resumo

**Introdução:** Ainda existem controvérsias em relação à melhor estratégia de terapia antitrombótica nos três meses iniciais de pós-operatório de implante de bioprótese valvar cardíaca. Assim, os autores consideram relevante determinar a incidência contemporânea de episódios de isquemia cerebral nos meses iniciais (primeiros 90 dias de pós-operatório), e realizar uma comparação entre a aspirina isolada *versus* a não terapia antiplaquetária no mesmo contexto.

**Métodos:** Entre o período de janeiro de 2010 a julho de 2012,

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#### Abbreviations, acronyms & symbols

ASA	Aspirin
CI	Confidence interval
ECG	Electrocardiogram
EuroSCORE II	European System for Cardiac Operative Risk Evaluation )
HR	Hazard ratio
PVT	Prosthetic valve thrombosis
STS	score Society of Thoracic Surgeons 2008 cardiac surgery risk model (the STS model) for isolated valve surgery
VKA	vitamin K antagonist

consecutivamente todos pacientes reumáticos com ritmo sinusal basal, que realizaram a substituição da valva mitral, e ou aórtica, por bioprótese (pericárdio bovino), foram incluídos neste estudo de coorte prospectivo, totalizando 184 pacientes. O desfecho primário avaliado foi a ocorrência de eventos embólicos.

## INTRODUCTION

Rheumatic heart disease is a major burden in developing countries where it causes most of the cardiovascular morbidity and mortality in young people, leading to about 250,000 deaths per year [1]. Unfortunately there is not a perfect valve substitute. The bioprosthesis valve has a theoretical great advantage: chronic anticoagulation is not mandatory in the absence of other risk factors [2]. Thus, this prosthesis is recommended when good quality anticoagulation is unlikely [2], unfortunately it is still a common situation for developing countries due the high incidence of chronic rheumatic disease in areas with low socioeconomic status [3,4].

There is still much debate regarding the kind of antithrombotic therapy in the immediate postoperative bioprosthesis period [4]. Thus, the aim of this study is to determine the contemporary incidence of thromboembolic events in rheumatic patients early after isolated aortic and mitral bioprosthesis replacement (in the first 90 days of the post-operative period), and perform a comparison between isolated use of Aspirin (ASA) with no-antiplatelet therapy, in this same context.

## METHODS

### Study Protocol

Between the period of January 2010 to July 2012, all consecutive rheumatic patients with basal sinus rhythm, who performed mitral and aortic valve replacement with bioprosthesis (pericardial bovine) in the cardiology service of Ana Nery Hospital in Salvador - Brazil, were classified as

**Resultados:** Nos primeiros 30 dias, três (5,2%) eventos isquêmicos cerebrais foram observados em pacientes do grupo aspirina, em comparação com dois (1,7%) eventos em pacientes sem terapia aspirina, RR = 3,18, 95% IC 0,5-19,6;  $P=0,33$ . Entre 31 e 90 dias do pós-operatório, nenhum paciente apresentou episódios de embolia cerebral ou periférica. A sobrevida livre de eventos embólicos, sangramentos e a sobrevida geral não foram estatisticamente significativas entre os grupos aspirina e não-aspirina.

**Conclusão:** Constatou-se baixa incidência de eventos embólicos durante os primeiros 90 dias de pós-operatório de troca valvar por bioprótese envolvendo a posição mitral, e uma ainda menor para mesma situação para troca aórtica isolada. O uso da aspirina não influenciou de maneira significativa na redução de episódios tromboembólicos.

**Descritores:** Aspirina. Acidente vascular cerebral. Bioprótese. Cardiopatia reumática.

poor candidates to chronic use of vitamin K antagonist (VKA) [5,6], and were included in this prospective observational single-center cohort study.

The main criteria used to classify a patient as a bad candidate to the use of VKA were the place of residence (rural or remote location of a hospital) and low socioeconomic level. The exclusion criteria were previous embolic events or atrial fibrillation, recent cerebral ischemia (6 months), coagulopathy, thrombophilia and allergies to ASA.

Preoperative surgical risk was quantified with the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) [7] and the Society of Thoracic Surgeons 2008 cardiac surgery risk model (the STS model) for isolated valve surgery [8].

In this cohort, despite being an open study, the investigators did not have any influence on the postoperative administration of ASA. Of three surgical teams that performed the surgical procedures, only one recommended the routine use of ASA in this context, and the other two teams opted not to use it. The selection of the surgical team for each patient always followed a computerized electronic scheduling, and this system, through a mechanism of random distribution of patients according to the demand of the service.

Clinical evaluation and follow-up after hospital discharge were performed by monthly consultations, by contacting the patients (patients who did not attend the scheduled appointments). Blood samples (blood count, renal function, electrolytes and coagulation) and ECG were carried out every 30 days. Those who presented any occurrence (for example atrial fibrillation, cerebral ischemia, bleeding events) were referred to the respective physician.

The primary endpoint was embolic events (ischemic stroke, transient cerebral ischemia or peripheral embolic event) in the first 90 days in the postoperative period. Secondary endpoints were prosthetic valve thrombosis, increase in functional NYHA class, need for a repeated operation, or death. Safety endpoint evaluated included bleeding as measured by GUSTO criteria [9].

To investigate prosthetic valve thrombosis (PVT), transthoracic echocardiography was performed 30 to 60 days after hospital discharge routinely, and transesophageal echocardiography, was performed to exclude suspected cases. All patients with confirmed PVT had urgent evaluation of cardiac surgery, and thrombolytic therapy when indicated.

In this study, the term cerebral ischemia was used to situations which a sudden, focal neurological deficit of presumed vascular origin lasting 24 hours to 7 days (reversible ischemic neurological deficit) or enduring more than 7 days (cerebrovascular accident), confirmed by computed tomographic or magnetic resonance scan imaging evaluated by a skilled physician. A peripheral embolism was diagnosed when there was a sudden onset of arterial occlusion in the extremities or sudden abdominal pain requiring urgent surgical intervention.

### Statistical Analysis

Baseline patient characteristics were stratified by treatment strategy and summarized as percentages for categorical variables and mean $\pm$ SD for continuous variables. All data were compiled and stored in a computerized database by a statistical package (SPSS Statistics 17.0.0 – IBM, Markham, Canada). Univariate analysis ( $X^2$  and  $t$  test) was used to compare categorical and numeric variables, respectively. Survival curves with the use of the Kaplan-Meier method were estimated to evaluate survival freedom from cerebrovascular accident, considering the time to the event consisted of the interval between 24 hours and 3 months after the surgery. Patients who did not experience a cerebrovascular accident and those who died were considered censored.

To test the hypothesis of equality between survival curves, the log-rank test was used. Hazard ratio (HR) was estimated to measure the association between group treatment and event, and 95% Confidence Interval (CI), was reported. A level of significance ( $\alpha=0.05$ ) was chosen for decision-making.

### RESULTS

A total of 184 consecutive rheumatic patients undergoing bioprosthesis that had been classified as bad candidates for chronic use of VKA previous to surgery, by local cardiology's team, were included in the study. Fifty nine patients received only ASA (100 mg/daily), starting on day 2 after surgery, and 125 patients did not use ASA therapy (up to 3 months in the postoperative period). There were no losses during follow-up, including death.

There were 90 male and 94 female patients. The mean age of the ASA group ( $45 \pm 16$  years) was similar with that of the no-ASA group ( $42 \pm 15$ ;  $P=0.25$ ). There were 27 cases (46%) of mitral stenosis in the ASA group *versus* 38 cases (30%) in no-ASA therapy ( $P=0.05$ ). Surgery to isolated aortic replacement were 16 cases (27%) and 39 (31%) in ASA and no therapy ( $P=0.57$ ). Distributions of aortic pathologies and mitral insufficiency were similar between the groups. There were no significant differences in gender distribution, prevalence of hypertension, diabetes and smoking (Table 1).

The STS stroke risk and mean left atrium diameter was similar in both groups: 0.36% *versus* 0.33% ( $P=0.56$ ) and 52 *versus* 51 mm ( $P=0.54$ ). Ninety-six percent of each therapeutic group were classified as low socio-economic status ( $P=0.98$ ), while 75% in both group lived in rural or remote areas ( $P=0.90$ ) (Table 1).

Table 1. Characteristics of patients at baseline (n = 184)

	ASA (n= 59)	Nothing (n= 125)	P Value
Male – no. (%)	24 (40)	66 (53)	0.13
Age, mean, y	$45 \pm 16$	$42 \pm 15$	0.13
Hypertension - no. (%)	16 (27)	27 (22)	0.48
Diabetes - no. (%)	2 (3.4)	3 (2.4)	0.73
Smoking - no. (%)*	21 (36)	33 (27)	0.25
Low socioeconomic status	57 (96)	120 (96)	0.98
Living remote areas†	44 (75)	94 (75)	0.90
Mitral pathology			
Mitral stenosis	27 (46)	38 (30)	0.05
Mitral insufficiency	40 (68)	75 (60)	0.31
Aortic pathology			
Aortic stenosis	13 (22)	24 (19)	0.65
Aortic insufficiency	20 (34)	48 (38)	0.55
Mitral replacement	43 (73)	86 (69)	0.57
Isolated aortic replacement	16 (27)	39 (31)	0.57
LVEF, mean, %	$62 \pm 12$	$60 \pm 14$	0.55
NYHA (III-IV) - no. (%)	56 (95)	100 (83)	0.02
Euroscore II, mean,%	$1.7 \pm 0.5$	$1.9 \pm 1.5$	0.37
STS stroke risk, mean,%	$0.36 \pm 0.26$	$0.33 \pm 0.37$	0.56
Left atrium, mean, mm	$52 \pm 10$	$51 \pm 13$	0.54

Values are number (%)=unless indicated otherwise; LVEF=indicates left ventricular

ejection fraction; NYHA=New York Heart Association

\* Previous or actual.

† Rural areas and small villages.

Primary, secondary and safely outcomes are reported in Table 2. All embolic occurred toward the brain. In the first 30 days of the postoperative period, three cerebral ischemia were observed among patients treated in the ASA group (5%) compared with two events in patients without ASA therapy (1.6%), HR=3.18; 95% CI 0.5 to 19.6;  $P=0.33$ . This represents an incidence rate of 0.57 *versus* 0.19 per 1000 patients/day (p/d), in each group, respectively. Between days 31 to 90 of follow-up, no patient had cerebral ischemia,

Table 2. Outcomes according study groups

	ASA (n=59)		Nothing (n=125)		Hazard Ratio (95% CI)	P Value
	No of Patients	Rate per 1000 person-day	No of Patients	Rate per 1000 person-day		
Primary endpoint: Stroke	3 (5)	0.57	3 (5)	0.57	3.18 (0.5-19.6)	0.33
Mitral replacement	3 (7)	0.82	3 (7)	0.82	2.27 (0.5-15.0)	0.11
Aortic replacement*	0	0	0	0	-	0.70
PVT: overall	1 (1.7)	0.19	1 (1.7)	0.19	0.96 (0.1-10.4)	0.99
Mitral replacement	1 (2.3)	0.27	1 (2.3)	0.27	0.96 (0.1-10.3)	0.98
Aortic replacement*	0	0	0	0	-	-
Death at follow-up‡	0	0	0	0	-	-
NYHA (I) at follow-up‡	58 (98)	-	58 (98)	-	0.99 (0.1-1.03)	0.58
Major bleeding§	0	0	0	0	-	-

Values are number (%)=unless indicated otherwise; AF=atrial fibrillation; LVEF=indicates left ventricular ejection fraction; PVT=prosthesis valve thrombosis; NYHA=New York Heart Association

\* Isolated aortic replacement.

† New documented Atrial Fibrillation at follow-up.

‡ Up to three months.

§ According GUSTO criteria.

regardless of ASA use. These rates, based on Kaplan-Meier estimates, were not statistically different between the two groups (Figure 1).

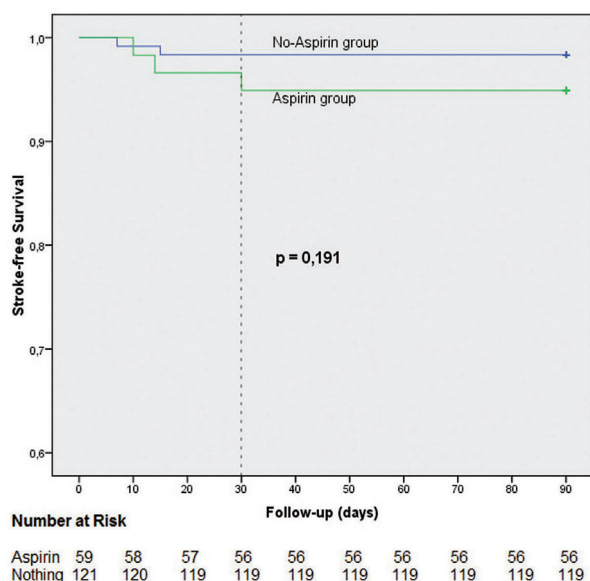


Fig. 1 - Stroke free survival

Patients with isolated aortic replacement in ASA group did not develop embolic event, while occurred one case in no-ASA Group, which represents an incidence rate of 0.08 per 1000 p/d for this latter. Patients who underwent mitral replacement, were observed three events of cerebral ischemia (0.82 per 1000 p/d) in ASA group, and only one in

no-antiplatelet group (0.08 per 1000 p/d);  $P=0.11$ . Prostheses valve thrombosis occurred only in mitral position. The overall rates were 0.19 ( $P=0.99$ ) in both groups.

Possible predictors to thromboembolic events, by including both therapeutic groups (ASA versus none), did not present statistically significant difference in univariate analysis.

## DISCUSSION

Rheumatic heart disease causes at least 200.000-250.000 premature deaths every year, and is the major cause of cardiovascular death in children and young adults in developing countries [3]. Prosthetic heart valves improve quality of life and survival of patients with severe valvular heart disease, but the need for antithrombotic therapy to prevent thrombotic complications in valve recipients poses challenges to clinicians and patients [1].

In this prospective cohort study of rheumatic patients, for the first time, a direct comparison between ASA versus no-antiplatelet therapy was performed, early after bioprosthesis replacement, not showing a significant difference in the incidence rate of embolic events during the first 30 days of the postoperative, with no events between 31 to 90 days of this same period. The person-time measurement used in this study was obtained through calculation (and not a direct measure), using the rate incidence. Since the outcome is not a continuous variable, we should be aware of its limitations.

The best evidence to date about antithrombotic management after aortic replacement was formed with the publication of a large-scale retrospective cohort study by Brennan et al. [10] with 25,656 patients and showed a low incidence of embolic events in the first 3 months of the



postoperative period (0.9%), a high variation of therapeutic strategy between various institutions, and no significant difference between patients treated with only warfarin *versus* patients treated only with ASA with respect to death, embolism and bleeding.

Guerli et al. [11] performed the first prospective study in this same scenario, and it indicated no statistically significant difference in the overall postoperative incidence of cerebral ischemia in both groups studied (warfarin *versus* ASA). Moinuddeen et al. [12] and Babin-Ebell et al. [13] showed similar results when assessing patients retrospectively. Brueck et al. [14] comparing ASA with no therapy in 288 consecutive patients with sinus rhythm did not find differences in the outcomes of functional status, embolic events and survival with 3 months of aortic bioprosthesis replacement. In mitral position, Colli et al. [15] conducted a retrospective small analysis with 99 patients comparing VKA, ASA and nothing, finding no difference between the three strategies evaluated.

The actual summary recommendation for antithrombotic therapy in the first 3 months after bioprosthesis surgery by the AHA/ACC is the use of ASA (class I/C) alone or combined with warfarin (class IIa/C), according to the presence or not of risk factors (atrial fibrillation, previous thromboembolism, left ventricular dysfunction, and hypercoagulable condition) [16]. The ESC and ACCP innovate when recommends the use of ASA (over warfarin) in the first 3 months for patients with bioprosthesis in aortic position, keeping the use of warfarin therapy to mitral position (class IIa/C and Grade IIc, respectively) [2,17]. This relatively low level of evidence present in all guidelines cited involving this issue is explained by the lack of large randomized clinical trials.

Although there is a general recommendation (in guidelines) for the utilization of anticoagulation therapy with warfarin in the first 3 months of the postoperative period, especially in the mitral position, there are significant variations of applications between cardiovascular centers around the world (Europe, Middle East, Canada and Asia), including some locations who do not use antithrombotic therapy in this situation [18].

In our study, the number of cerebral events in the ASA group was almost double that in patient with no antiplatelet therapy in the first 30 days, without statically significance. This absolute difference can be explained by the small sample, absence of a true randomization or by the more prevalence of mitral stenosis in the ASA group that could lead to more episodes of atrial fibrillation and subsequent more embolic events. Finally, the fact that the patients had been operated by three different surgical teams may also have affected the rate of embolic events in the short and medium term.

Healey et al. [19] showed that subclinical atrial tachyarrhythmias, without clinical atrial fibrillation, occurred frequently in patients with pacemakers and were associated

with a significantly increased risk of ischemic stroke or systemic embolism, and Olesen et al. [20] in a large cohort study, in patients with non-valvular atrial fibrillation, showed that ASA treatment has no effect on the risk of stroke/thromboembolism.

## CONCLUSION

In conclusion, in this prospective cohort of rheumatic patients, we found a low and very rare incidence rate of embolic events during the first 90 days of the postoperative period, in mitral and isolated aortic replacement, respectively. The use of aspirin did not significantly influence the rate of thromboembolism.

### Authors' roles & responsibilities

ARD	Study design, protocol execution, data analysis and manuscript writing
MAOD	Data collection and study design
LCC	Statistical analysis and manuscript review
AMSF	Data collection
RAJ	Study design, data analysis and manuscript review

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