

Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively: DAWA Pilot Study

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Abstract

Objectives Dabigatran is a direct thrombin inhibitor shown to be an effective alternative to warfarin in patients with non-valvular atrial fibrillation (AF). We evaluated the use of dabigatran in patients with bioprosthetic mitral and/or aortic valve replacement and AF.

Methods We selected 34 and randomized 27 patients in a 1:1 ratio to receive dabigatran or warfarin. The primary endpoint was the presence of a new intracardiac thrombus at 90 days, by transesophageal echocardiogram (TEE). Secondary endpoints included the development of dense spontaneous echo contrast (SEC) and incidence of stroke (ischemic or hemorrhagic), myocardium infarction, valve thrombosis and peripheral embolic events.

Results The trial was terminated prematurely because of low enrollment. There were 27 patients in total: 15 patients placed in the dabigatran group and 12 in the warfarin

group. After 90 days, one patient (8.3 %) in the warfarin group and none in the dabigatran group had developed a new intracardiac thrombus. In the dabigatran group, two patients (13.3 %) developed dense SEC versus one patient (8.3 %) in the warfarin group. In the warfarin group, one patient (8.3 %) presented ischemic stroke, and none did in the dabigatran group. We observed no cases of hemorrhagic stroke, valve thrombosis, embolic events or myocardial infarction in either group throughout the study. However, one patient (6.7 %) in the dabigatran group had a fully recovered transient ischemic attack and one patient in the warfarin group died of heart failure.

Conclusions The use of dabigatran appears to be similar to warfarin in preventing the formation of intracardiac thrombus.

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Key Points

There are no published study in humans evaluating the efficacy and safety of dabigatran or any other NOACs in patients with mitral and/or aortic bioprosthesis valve.

DAWA is a phase 2, prospective, open-label, randomized, pilot study. The main variable to be observed in this study is intracardiac thrombus. There are no formal primary or secondary clinical efficacy or safety outcomes because it is a pilot study.

The DAWA study encourages a larger multicentric prospective study to assess the use of new oral anticoagulants in patients with bioprosthesis valve.

1 Introduction

Thromboembolism and anticoagulant-related bleeding represent the majority of complications experienced by prosthetic valve recipients. It is estimated that 4 million valve replacement procedures have been performed in the last 50 years and it remains the only definitive treatment for most patients with advanced heart valve disease [1]. Oral anticoagulation with warfarin and similar vitamin K antagonists (VKAs) is recommended lifelong for patients with bioprosthesis who have other indications for anticoagulation, such as atrial fibrillation (AF) [2]. 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. Because of VKAs' narrow therapeutic index, interactions, genetic variants, and need for blood monitoring of patients, different anticoagulants with more predictable pharmacological effects have been searched for. Alternatives to warfarin are now available [3].

Dabigatran etexilate is the prodrug of dabigatran, a direct thrombin (factor IIa) inhibitor, which was approved by the US Food and Drug Administration (FDA) for the prevention of stroke and systemic embolism in patients with nonvalvular AF, and has also been approved for the treatment of acute deep vein thrombosis and pulmonary embolism. Antithrombotic therapy for thromboprophylaxis in patients with mechanical heart valves remains challenging [4, 5]. Until now, the Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial [6] comparing dabigatran etexilate to warfarin was the only randomized controlled study in patients with mechanical valve prosthesis, but it was terminated prematurely because of an excess of thromboembolic and bleeding events among patients in the dabigatran group. Additional studies are needed to find suitable alternatives to VKAs in this population [7]. There are no published studies in humans evaluating the efficacy and safety of dabigatran or any other new oral anticoagulant (NOAC) in patients with mitral and/or aortic bioprosthesis valve. The Dabigatran Versus Warfarin After Bioprosthesis Valve Replacement for the Management of Atrial Fibrillation Postoperatively (DAWA) study was designed to provide the first clinical trial that tested dabigatran use in patients with bioprosthesis and AF postoperatively.

2 Methods

2.1 Study Design and Oversight

DAWA is a phase II, prospective, open-label, randomized, pilot study. The main variable to be observed in this study

is intracardiac thrombus. There are no formal primary or secondary clinical efficacy or safety outcomes because it is a pilot study. Mortality and morbidity events (reversible ischemic neurological deficit, ischemic and hemorrhagic stroke, systemic embolism, any bleeding, prosthesis valve thrombosis and death) were evaluated in an exploratory manner. The details of the trial design have been previously described [8]. The trial protocol was approved by the local ethics and research committee in the city of Salvador-Brazil (under protocol number 14284813.9.0000.0045), and written informed consent was obtained from all patients. An independent data and safety monitoring board closely monitored the trial. All the authors contributed to the interpretation of the results, wrote the first version of the manuscript and approved all versions, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data reported and the fidelity of this article to the study protocol.

2.2 Patients and Randomization

Patients eligible for inclusion in the study were 18–64 years old, underwent mitral and/or aortic bioprosthesis valve replacement at least 3 months prior to entering the study and had documented AF postoperatively in addition to exclusion of atrial thrombus or valve prosthesis thrombosis by transesophageal echocardiogram (TEE). Non-contrast brain computed tomography (CT) without hemorrhage or findings of acute cerebral infarction on the last 2 days of screening was also necessary. The complete list of inclusion and exclusion criteria is provided in the protocol [8].

Patients were randomly assigned to receive dabigatran or warfarin by a computer generated list of random numbers performed to a 1:1 ratio between the groups. Following that, the allocation sequence was concealed from the researcher enrolling participants in sequentially numbered, opaque, black, sealed envelopes. After randomization, patients had study visits scheduled at 7 days (via telephone) and at 30 days (personally), with a monthly follow-up for 90 days. After this, non-contrast brain CT (or magnetic resonance imaging when necessary) and TEE were repeated in all randomized patients. The former was executed to document possible cerebral events with no clinical expression and the latter to analyze the incidence of intracardiac thrombi, new dense spontaneous echo contrast (SEC) or its resolution, in addition to thrombosis or dysfunction of valvular prosthesis.

2.3 Drug Administration Protocol

Patients assigned to the dabigatran group received 110 mg of dabigatran etexilate twice daily. Patients with previous

use of warfarin underwent washout with immediate introduction of dabigatran once the international normalized ratio (INR) was <2.5 . The warfarin dose was adjusted to maintain the INR between 2.0 and 3.0. Doses were between 5 and 10 mg in the first days for most individuals, with subsequent dosing based on INR response.

2.4 Outcomes

The primary endpoint was the detection of intracardiac thrombus in TEE at the end of follow-up (90 days). Additional efficacy and safety outcomes included dense SEC, stroke (ischemic or hemorrhagic), reversible ischemic neurological deficit, systemic embolism, prosthesis valve thrombosis, bleeding event (major or minor), elevated liver enzymes or hepatic function abnormalities and death.

TEE was performed using a commercially available ultrasound imaging system (iE33; Philips Medical Systems, Andover, MA, USA) with a 3-dimensional matrix-array transesophageal transducer. Left atrial (LA) abnormalities such as thrombus and dense SEC were assessed by TEE in all patients. Dense SEC was defined as a dynamic smoke-like signal that swirled slowly in a circular pattern within the LA and appendage, with a gradation of $>2+$ [9, 10].

The bleeding risk was based on the criteria of the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis [11] and HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) score [12].

2.5 Statistical Considerations

The SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis of the collected data. The primary analysis was performed according to the intent-to-treat principle. A safety analysis was performed on all patients treated, regardless of any protocol violations. Quantitative variables were described as mean and standard deviation. The mean comparison was performed by the Student *t* test for independent populations or related populations, as appropriate. The qualitative and categorical variables were presented as percentages, and their comparisons were made by the Fisher exact test.

3 Results

3.1 Study Discontinuation

The data and safety monitoring board recommended discontinuation of the study on September 1, 2014 because of

a significant drop in recruitment. All participating patients discontinued the assigned study drug and were switched to warfarin.

3.2 Patients and Follow-Up

A total of 34 patients were selected between August 2013 and November 2014 (six were excluded for previous intracardiac thrombus; one for unstable INR control). Of the 27 randomized, 15 were assigned to receive dabigatran and 12 to receive warfarin. The characteristics of the patients at baseline were well balanced (Table 1). The majority of patients were female (66.7 and 58.3 %), young adults (mean 48.8 ± 10.4 and 45.7 ± 6 ; median 45 and 44.5) who had undergone isolated mitral valve replacement (73.3 and 75 %), with few risk factors in both groups (hypertension 46.7 and 50 %; diabetes 7.1 and 0 %; smoking 13.3 and 25 %; previous stroke 26.7 and 33.3 %), and with low-risk surgery (logist euroSCORE mean $1.6 \% \pm 0.4$ and $1.9 \% \pm 1.5$), in the dabigatran and warfarin groups, respectively (Table 1). One patient did not finish the follow-up because he/she died. All others made use of the randomized drug by the scheduled period (up of 90 days).

3.3 Clinical Outcomes

Intracardiac thrombus occurred in one patient (8.3 %) in the warfarin group. One case (8.3 %) of ischemic stroke occurred in the warfarin group, and one case (6.7 %) of reversible ischemic neurological deficit was observed in the dabigatran group. Bleeding occurred in one patient in the dabigatran group (6.7 %) and two patients (16.7 %) in the warfarin group, respectively. One case of hospitalization in each group was seen, without statistical significance (Table 2).

Dense SEC was detected in seven patients (46.7 %) in the dabigatran group and three patients (25 %) in the warfarin group [hazard ratio 0.38; 95 % confidence interval (CI) 0.10–2.00; $P = 0.23$] at the end of the study. Resolution and new SEC occurred in one (6.7 %) versus one patient (8.3 %) (hazard ratio 1.30; 95 % CI 0.10–22; $P = 0.70$) and two (13.3 %) versus one patient (8.3 %) (hazard ratio 0.60; 95 % CI 0.10–7.4; $P = 0.58$) in the dabigatran and warfarin groups, respectively (Table 3).

4 Discussion

Utilizing the good accuracy of TEE for detecting LA thrombi and brain CT scans in the detection of ischemic and hemorrhagic cerebrovascular events, we compared dabigatran 110 mg twice daily with adjusted-dose warfarin,

Table 1 Baseline characteristics

	Dabigatran (<i>n</i> = 15)	Warfarin (<i>n</i> = 12)
Male, no. (%)	5 (33.3)	5 (41.7)
Age (years)		
Mean	48.8 ± 10.4	45.7 ± 6
Median	45	44.5
Range	37–67	37–54
Hypertension, no. (%)	7 (46.7)	6 (50)
Diabetes, no. (%)	1 (7.1)	0
Smoking, no. (%) ^a	2 (13.3)	3 (25)
Previous stroke	4 (26.7)	4 (33.3)
Isolated mitral replacement	11 (73.3)	9 (75)
LVEF, mean (%)	40 ± 12	50 ± 10
NYHA (III–IV), no. (%)	5 (33.3)	3 (27.3)
Logistic euroSCORE II, mean (%) ^b	1.6 ± 0.4	1.9 ± 1.5
Left atrium, mean (mm)	58 ± 10	53 ± 13
HAS-BLED ^c , median	0 (0–1)	0 (0–1)

Plus-minus values are means ± SD. No significant differences were noted between the groups

HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association *SD* standard deviation

^a Previous or actual

^b The logistic European System for Cardiac Operative Risk Evaluation (euroSCORE), which measures risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. A score of >20 indicates a very high surgical risk

^c A score of ≥3 suggests increased bleeding risk and warrants some caution and/or regular review

Table 2 Efficacy and safety outcomes, according to treatment group

Event	Dabigatran (no. of patients)	Warfarin (no. of patients)	Relative risk (95 % confidence interval)	<i>P</i> value
Intracardiac thrombus	0	1 (8.3)	1.1 (0.9–1.3)	0.42
Stroke or systemic embolism	0	1 (8.3)	1.1 (0.9–1.3)	0.44
Reversible ischemic neurological deficit	1 (6.7)	0	0.9 (0.8–1.0)	0.55
Bleeding ^a	1 (6.7)	2 (16.7)	2.8 (0.2–35)	0.41
Hospitalization	1 (6.7)	1 (8.3)	1.3 (0.7–22)	0.70
Death	0	1 (8.3)	1.1 (0.9–1.3)	0.44

Values are number (%) unless indicated otherwise

HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol, *NA* not applicable

^a According criteria of Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis and HAS-BLED score

administered in an unblinded fashion, in patients at least 3 months after bioprosthesis replacement and with AF post-operatively, having as the main goal the detection of intracardiac thrombus. However, the trial was stopped early because of a significant decrease of eligible candidates for recruitment. Among the most important reasons for this, we detected a high rate of intracardiac thrombus in the selection phase, low socioeconomic status in many

others, and addition to the negative results of the Re-align study.

Despite the small sample size of this randomized pilot study, to the best of our knowledge, our current study is the first that has held a direct comparison between an NOAC (dabigatran) and warfarin in patients with a bioprosthesis valve and AF until now. The primary and all secondary endpoints had quantitatively few events in both groups.

Table 3 Spontaneous echo contrast and TTR analysis

Event	Dabigatran (no. of patients)	Warfarin (no of patients)	Relative risk (95 % confidence interval)	<i>P</i> value
Dense SEC				
At baseline	6 (40)	3 (25)	0.50 (0.1–2.6)	0.34
At the end	7 (46.7)	3 (25)	0.38 (0.1–2.0)	0.23
Resolution of SEC ^a	1 (6.7)	1 (8.3)	1.30 (0.1–22)	0.70
New SEC ^b	2 (13.3)	1 (8.3)	0.60 (0.1–7.4)	0.58
Mean TTR (%)	NA	66.5 ± 7	NA	NA

Values are number (%) unless indicated otherwise

NA not applicable, SEC spontaneous echo contrast, TEE transesophageal echocardiogram, TTR time in therapeutic range

^a SEC positive and negative in the first and last TEE, respectively

^b SEC negative and positive in the first and last TEE, respectively

The bioprosthesis emerged last century with the expectation of replacing existing mechanical prosthesis, due to not theoretically requiring permanent oral anticoagulation. Actually, the recommendations of the main international guidelines on antithrombotic therapy after bioprosthesis implantation demonstrate a low level of evidence (Grade C), which may be explained by the lack of randomized trials in this scenario [13].

However, certain patients with bioprosthesis may require long-term anticoagulant therapy when there are other indications, in particular with AF. In these cases, thrombogenicity is due to AF and not to the prosthesis. It can be expected that the current absence of indication of NOACs for mechanical prosthesis will be an incentive to continue, or even strengthen, the trend towards favoring implantations of bioprosthesis at the expense of mechanical valves [14].

The reason for evaluating the formation of thrombus or SEC by TEE is justified since they are independent predictors for thromboembolic events, as evidenced in several previous studies. About 30–60 % of patients with SEC or intracardiac thrombus evolve with major thromboembolic events [15]. Patients with AF and dense SEC have a high likelihood of cerebral embolism (22 %) and/or death, despite oral anticoagulation [16]. Furthermore, microembolization of small thrombi derived from the fibrillating LA may be significant causes of silent brain infarction in nonvalvular AF patients [9].

Regarding the dosage of dabigatran 110 mg twice a day chosen in this study, it was based on the results of the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial, which showed no significant difference in stroke or mortality, but a higher rate of major bleeding with the higher versus lower dabigatran dose (150 vs. 110 mg twice a day, respectively) and no difference between the doses in net

clinical benefit as estimated by the composite of stroke, bleeding and death [17]. Recently, a separate analysis of the two low-dose NOAC regimens (which included dabigatran) showed that although they have a similar efficacy to warfarin for protection against all stroke or systemic embolic events, they are not as effective for protection against ischemic stroke in particular. However, they do have a safer profile than warfarin and preserve the mortality benefit noted with the high-dose regimens [18].

Beyond that, it is possible that patients with AF and bioprosthesis or valve repair have a risk of thromboembolism not substantially different from that with more common forms of ‘non-valvular’ AF, and in any case, on the basis of preliminary evidence accrued from trials with NOACs, there is no evidence of different efficacy or safety compared with warfarin [19].

About neurological events, in the RE-ALIGN study [6], it is important to see that most thromboembolic events among patients in the dabigatran group occurred in ‘population A’ (patients who had started a study drug within 7 days after valve surgery), with fewer occurring in ‘population B’ (patients who had undergone valve implantation more than 3 months before randomization). Besides, stroke, death and major bleeding occurred only in the first group. All patients in our study have more than a 3-month interval from surgery for recruitment, a period known to have a lower incidence of embolic events [20].

There are several limitations of DAWA, among which we highlight the following: unicentric pilot study; small sample size; and short follow-up (90 days) for the occurrence of major clinical events. Despite this, it can be very useful as a hypothesis generator for a large randomized trial.

In summary, the DAWA study encourages a larger multicentric prospective study to assess the use of this NOAC in such a population (bioprosthesis) since usual

doses would be enough to avoid the formation of thrombi and its several complications, including hard endpoints such as prosthesis thrombosis, stroke or major bleeding.

Compliance with Ethical Standards

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