# Back to sinus rhythm from atrial flutter or fibrillation: dabigatran is safe without transoesophageal control

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# Abstract

**Background and aim:** To assess the safety of dabigatran in converting persistent atrial fibrillation (PAF) and atrial flutter (AFL) to sinus rhythm (SR) without transoesophageal echocardiography (TEE) evaluation.

**Methods:** Consecutive patients with PAF or AFL were included between 2012 and 2015. Dabigatran was used for three weeks before and six months after cardioversion. Left atrium area (LAA) and left atrium volume (LAV) were assessed in all patients. Follow-up visits for major cardiac events occurred at 1, 3, 6, and 12 months.

**Results:** The study included 82 patients (56 male, mean age 63.1  $\pm$  10.4 years), of which 45 had PAF and 37 AFL. In patients with PAF, mean LAA was 30.3  $\pm$  5.3 cm<sup>2</sup> and LAV 114.4  $\pm$  31.5 mL; in those with AFL mean LAA was 26.5  $\pm$  4.2 cm<sup>2</sup> and LAV 97  $\pm$  24.9 mL at baseline. Forty-nine patients underwent uncomplicated electric cardioversion (38 with PAF and 11 with AFL), 11 patients were pharmacologically converted to SR (7 with PAF and 4 with AFL), and 22 patients with AFL underwent successful radiofrequency ablation. The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 2.96  $\pm$  1.39 (score > 3, 58.6%). No major cardiac events occurred during the follow-up period of 19.4  $\pm$  9.5 months.

Conclusions: Safe cardioversion using dabigatran was achieved in this small group of patients without the need for TEE.

Key words: transoesophageal echocardiography, atrial flutter or fibrillation, dabigatran

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#### **INTRODUCTION**

Warfarin, a vitamin K epoxide reductase inhibitor, is the most widely used oral anticoagulant since the 1950s. It improves survival of patients with persistent atrial fibrillation (PAF) and in high-risk patients converted to sinus rhythm (SR) [1]. On the other hand, warfarin, is known to interact with food and drugs and therefore requires regular laboratory monitoring. In addition, its effective half-life is rather long, ranging from 20 h to 60 h. By contrast, dabigatran, a target-specific oral anticoagulant, has a serum half-life of 12 h to 17 h [2], does not require regular monitoring, and is not inferior to warfarin in treating patients with nonvalvular PAF [3]. Appropriate patient selection was associated with higher dabigatran adherence [4] than that published for warfarin [5]. Indeed, a retrospective study of more than 4000 single-centre direct current cardioversion (DCCV) procedures performed between 2009 and 2013 showed that

non-warfarin anticoagulant utilisation, including dabigatran, is used in over one third of cardioversion procedures, and these agents have similarly low rates of thromboembolic and bleeding complications when compared with warfarin [6]. Regardless of the method used to achieve SR, current European Society of Cardiology guidelines recommend three to four weeks of adequate anticoagulant therapy (warfarin with international normalised ratio [INR] 2–3 or dabigatran) before cardioversion in patients with atrial fibrillation (AF) or atrial flutter (AFL) [7].

Transoesophageal echocardiography (TEE) is used frequently to visualise the left atrium and its appendage and search for thrombi or spontaneous echocardiographic contrast in the setting of cardioversion. Nevertheless, its value in predicting the risk of stroke or embolic events is not established and earlier studies suggest that patient history may be a better indicator of embolic risk [8].

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The aim of the present study was to asses the safety of dabigatran treatment associated with conversion of PAF or AFL to SR in a real-world clinical practice patient population, without performing follow-up TEE.

## METHODS Patients

Patients

The patient population in this retrospective cohort study included consecutively hospitalised patients for PAF or AFL treated with dabigatran, and in whom SR was obtain either by DCCV, conventional typical AFL ablation, or oral antiarrhythmic drugs. Patient selection criteria included: hospitalisation for PAF or AFL and discharge with normal SR; unstable INR values; patients in whom INR monitoring was not feasible (no access to regular INR monitoring); and patients who preferred dabigatran to warfarin therapy. Exclusion criteria were severe valvular disease including stenosis and/or regurgitation, previous AF ablation, peri-procedural TEE, AF due to a reversible cause, serum creatinine level > 2.5 mg/mL, and associated severe morbidity (hepatic or renal failure, pulmonary, cerebral, etc.).

### Dabigatran administration

Dabigatran was administered for at least three weeks before DCCV/AFL ablation and six months after cardioversion. Patients were monitored for a minimum of six months after DCCV to evaluate embolic risk, including stroke, transient ischaemic attack, and death. Follow-up visits for major cardiac events occurred at 1, 3, 6, and 12 months after cardioversion, and yearly thereafter. Major and minor bleeding was also monitored.

Participants were followed for  $19.4 \pm 9.5$  months from the date of cardioversion. Major cardiac-vascular events were defined as stroke, systemic or pulmonary embolism, myocardial infarction, major bleeding, and death. We considered major bleeding as proposed by the International Society of Haemostasis and Thrombosis: bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two units of packed red blood cells, fatal bleeding, or symptomatic bleeding in a critical area or organ (e.g. intracranial, intraspinal, pericardial) [9]. All other bleedings were considered minor.

# Echocardiographic examination

Transthoracic echocardiography was performed in all patients at baseline. Ultrasound images were explored with patients in the left lateral decubitus position, using a GE VIVID 7/9 machine (Vivid 7, GE Health Medical, Milwaukee, WI, USA). Electrocardiogram (ECG) was simultaneously recorded for each patient. The echocardiographic examination was performed using standard views and techniques [10]. Standard echocardiographic measurements included interventricular septum, left ventricular end-diastolic diameter and volume, and left ventricular ejection fraction (Simpson's method); left atrial (LA) diameter was measured by M-mode in the parasternal long-axis view, and LA area (LAA) and LA volume (LAV) were measured in the apical four-chamber view. All LA measurements were performed at end-systole just before mitral valve opening and maximal atrium size was considered for evaluation [10]. Mean arterial pressure was calculated as: MAP = 2/3 diastolic arterial pressure + 1/3 systolic arterial pressure.

### Statistical analysis

Baseline clinical and demographic features are presented as means or percentages ( $\pm$  standard deviation) in Table 1. Baseline echocardiographic parameters are presented as means ( $\pm$  standard deviation) and range in Table 2. Echocardiographic parameters were compared between subjects with PAF and AFL by analysis of covariance for continuous variables. All analyses were performed using IBM SPSS, version 19 (SPSS Inc., Chicago, Illinois).

#### RESULTS

This study included 82 patients (56 male, mean age 63.1  $\pm$  10.4 years), of which 45 had PAF and 37 AFL. Their demographic and clinical characteristics are presented in Table 1.

Sixty-five (79.2%) patients received dabigatran 150 mg twice daily, and 17 patients received dabigatran 110 mg twice daily (3 patients > 80 years old, 14 patients with creatinine clearance 30-50 mL/min). None of the patients included in the present study used aspirin.

The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was  $2.96 \pm 1.39$  (score > 3 in 58.6% patients). Distribution of CHA<sub>2</sub>DS<sub>2</sub>-VASc score for age groups is presented in Figure 1.

All PAF patients had moderate to severe LA dilatation: LAA 30.3  $\pm$  5.3 cm<sup>2</sup>, LAV 114.4  $\pm$  31.5 mL (LAA range 20– -42 cm<sup>2</sup>, LAV range 50–190 mL); patients with AFL presented lower LA values: LAA 26.5  $\pm$  4.2 cm<sup>2</sup> and LAV 97  $\pm$  24.9 mL (LAA range 16–38 cm<sup>2</sup>, LAV 40–170 mL) (Table 2).

Uncomplicated DCCV was performed in 38 PAF patients and 11 AFL patients. Pharmacologic conversion was attained in seven PAF and four AFL patients (five PAF patients with oral flecainide 100 mg one a day and the others with amiodarone administered orally 200 mg one a day, after loading according to guidelines). Twenty-two AFL patients underwent successful radiofrequency ablation. Recurrence of PAF was noted in nine patients during the follow-up period; four of these patients were left in permanent AF at the end of this study after a second attempt of DCCV failed, and were subsequently treated with antiarrhythmic drugs (oral metoprolol succinate with controlled release 100 mg one a day). Among patients with AFL, five experienced recurrence (2 DCCV) with successful consecutive radiofrequency ablation. There were no major cardiac events, no embolic events, major bleeding

	All patients (n = 82)	PAF (n = 45)	AFL (n = 37)
Mean age [years]	63.1 ± 10.4	63.4 ± 9.1	62.8 ± 12
Mean follow-up [months]	$19.4\pm9.5$	$19.2 \pm 9.4$	$19.7 \pm 9.7$
Male	56 (68.2%)	29 (64.4%)	27 (72.9%)
Hypertension	60 (73.1%)	31 (68.8%)	29 (78.3%)
Diabetes mellitus	15 (18.2%)	6 (13.3%)	9 (24.3%)
Transient ischaemic attack or cerebrovascular accident	7 (8.5%)	3 (6.6%)	4 (10.8%)
Coronary artery disease*	6 (7.3%)	3 (6.6%)	3 (8.1%)
Dilated cardiomyopathy	11 (13.4%)	5 (11.1%)	6 (16.2%)
Chronic kidney disease**	32 (395)	17(37.7%)	15 (40.5%)

Table 1. Baseline features of patients with persistent atrial fibrillation (PAF) or atrial flutter (AFL) included in the study

\*Coronary artery disease = documented angina/myocardial infarction; \*\*Chronic kidney disease defined as reduction in creatinine clearance < 90 mL/min. None of the patients in our cohort had creatinine clearance < 30 mL/min

Table 2. Main transthoracic echocardiographic characteristics at baseline

Echocardiographic	All patients (n = 82)		PAF group (n = 45)		AFL group (n = 37)		Р*
parameters	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Interventricular septum [mm]	12.9 ± 2.2	10.0–23.0	$13.2\pm2.4$	10.0–23.0	$12.5 \pm 1.9$	10.0-22.0	0.19
Ejection fraction [%]	$47.4\pm7.6$	25.0-60.0	$49.4\pm7.2$	25.0-60.0	$44.9 \pm 7.4$	25.0-55.0	0.01
LV end-diastolic diameter [cm]	$5.0\pm0.8$	3.9–7.9	$4.9\pm0.7$	4.0-7.9	$5.0\pm0.8$	3.9–7.8	0.70
LV end-diastolic volume [mL]	$122.0 \pm 51.9$	60.0–330.0	$123.9 \pm 51.6$	70.0–330.0	121.1 ± 54.5	60.0-300.0	0.90
LA diameter [cm]	$4.5\pm0.6$	3.4–6.7	$4.6\pm0.6$	3.6-6.7	$4.4\pm0.6$	3.4–5.6	0.20
LA area [cm <sup>2</sup> ]	$28.7\pm5.2$	16.0-42.0	$30.3\pm5.3$	20.0-42.0	$26.5\pm4.2$	16.0–38.0	0.001
LA volume [mL]	$106.8\pm29.9$	40–190	114.4 ± 31.5	50.0-190.0	97 ± 24.9	40.0-170.0	0.01

\*P values for comparisons between PAF and AFL groups. AFL — atrial flutter; LA — left atrial; LV — left ventricular; PAF — persistent atrial fibrillation

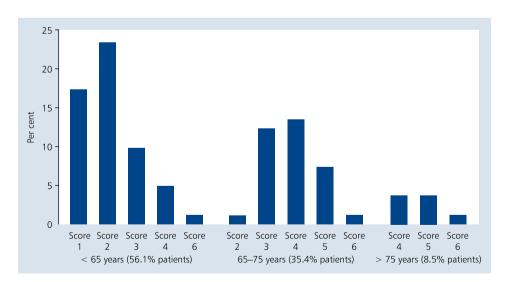


Figure 1. Distribution of CHA, DS, -VASc score by age groups in 82 patients on dabigatran

events, or deaths during the follow up period. Minor bleeding occurred in two patients and did not require discontinuation of dabigatran therapy.

# DISCUSSION

In the present patient cohort with moderate to severe LA dilatation and average CHA,DS<sub>2</sub>-VASc score of 2.9, mid-term

anticoagulation with dabigatran was safe after cardioversion for PAF or AFL. Follow-up TEE was not performed and no major or minor events were observed, even though the CHA<sub>2</sub>DS<sub>2</sub>-VASc score was higher than that reported in the RELY trial [3]. These results suggest that invasive monitoring practices are not essential with dabigatran in carefully selected patients.

Information about dabigatran safety without follow-up TEE control three weeks after newly converted PAF or AFL is sparse in the literature. Compulsory follow-up TEE is being performed on the grounds of the relatively frequent occurrence of spontaneous echocardiographic contrast and thrombi in the LA of patients with PAF and their associations with stroke or embolic events [11, 12]. Nevertheless, a prospective, multicentre study including patients with AF and without recent history of stroke showed that age, hypertension, and previous stroke were stronger risk factors for embolic events than size of the LA, or the presence of thrombi in the LA or LA appendage. This suggests that selecting patients based on risk factor history may be at least as useful in assessing risk for embolism as TEE [8, 13]. The utility of TEE in the setting of cardioversion and related anticoagulation is more evident in patients with recent history of embolism, valvular disease, and absolute indication for anticoagulation [13].

Novel oral anticoagulants such as dabigatran, apixaban, and rivaroxaban are all recommended alternatives to warfarin in select patients undergoing cardioversion, with a class IIa indication in the latest American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines [14]. For dabigatran this recommendation is largely based on results from the RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial [15, 16] and a meta-analysis of non-inferiority randomised trials [17]. Indeed, the guidelines acknowledge that treatment effects of direct thrombin or factor Xa inhibitors are based on limited cohort studies and need further evaluation of safety and efficacy in patients with nonvalvular AF (a level of evidence C) [14]. The current study adds to the existing evidence, proposing that dabigatran treatment can be safely used without TEE control in selected patients undergoing cardioversion.

The generalisability of our results is limited by the relatively small number of patients and the availability of data limited by the retrospective design, and may not apply to more racial/ethnic diverse populations. Nonetheless, these patients are rigorously selected for dabigatran treatment, are well characterised clinically, and have been followed for treatment complications for six months after cardioversion. Furthermore, although the cost of dabigatran is higher than of warfarin, recent analyses have indicated that dabigatran 150 mg is a cost–effective alternative to warfarin for elderly patients with high risk for stroke [18, 19]. Whether this is the case for lower risk patients, such as those included in the present study and in different health care systems, is not known [20].

# COCLUSIONS

In conclusion, dabigatran is effective in the prevention of thromboembolism and is safe in patients with PAF or AFL undergoing cardioversion. Moreover, dabigatran usage in this setting was safe in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score higher than 2, without the need for TEE.

# Conflict of interest: none dclared

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# Przywrócenie rytmu zatokowego w trzepotaniu lub migotaniu przedsionków: dabigatran jako bezpieczny lek niewymagający kontroli za pomocą echokardiografii przezprzełykowej

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# Streszczenie

Wstep i cel: Badanie przeprowadzono, aby przeanalizować bezpieczeństwo stosowania daibatranu w przywracaniu rytmu zatokowego (SR) u chorych z przetrwałym migotaniem przedsionków (PAF) i trzepotaniem przedsionków (AFL) bez oceny za pomoca echokardiografii przezprzełykowej (TEE).

Metody: Do badania właczono kolejnych chorych z PAF lub AFL w okresie od 2012 do 2015 r. Dabigatran stosowano 3 tygodnie przed kardiowersją i 6 miesięcy po kardiowersji. U wszystkich pacjentów zmierzono pole powierzchni (LAA) i objętość (LAV) lewego przedsionka. Wizyty kontrolne w celu oceny występowania poważnych zdarzeń sercowych odbywały się po 1, 3, 6 i 12 miesiącach.

Wyniki: Badanie obejmowało 82 chorych (56 mężczyzn, średnia wieku 63,1 ± 10,4 roku), w tym 45 osób z PAF i 37 z AFL. Na początku badania u pacjentów z PAF średnie LAA wynosiło 30,3 ± 5,3 cm<sup>2</sup>, a średnia LAV — 114,4 ± 31,5 ml, natomiast u chorych z AFL średnie LAA wynosiło 26,5 ± 4,2 cm², a średnia LAV — 97 ± 24,9 ml. Czterdziestu dziewięciu chorych poddano niepowikłanej kardiowersji elektrycznej (38 osób z PAF i 11 osób z AFL), u 11 pacjentów przywrócono SR, stosując kardiowersję farmakologiczną (7 osób z PAF i 4 osób z AFL), a u 22 chorych z AFL wykonano skuteczną ablację prądem o wysokiej częstotliwości. Średnia punktacja w skali CHA,DS,-VASc wynosiła 2,6  $\pm$  1,39 (58,6% chorych z punktacją > 3). W trwającej 19,4 ± 9,5 miesiąca obserwacji nie odnotowano poważnych zdarzeń sercowych.

Wnioski: Stosowanie dabigatranu pozwoliło uzyskać w tej niewielkiej grupie pacjentów skuteczną kardiowersję bez konieczności wykonania TEE.

Słowa kluczowe: echokardiografia przezprzełykowa, trzepotanie lub migotanie przedsionków, dabigratran

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