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Original Article

Left atrial thrombus formation and resolution during dabigatran therapy: A Japanese Heart Rhythm Society report

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ABSTRACT

Background: Protocols on the use of novel oral anticoagulants for stroke prevention in patients with atrial fibrillation (AF) undergoing electrical cardioversion (ECV) are lacking.
Aim: The study was aimed at evaluating the efficacy of dabigatran (Dabi) treatment in preventing peri-ECV stroke.
Methods: A retrospective survey of the incidence and fate of left atrial (LA) thrombus during Dabi therapy in patients with AF was conducted between December 2012 and January 2013 by the Japanese Heart Rhythm Society.
Results: A total of 198 patients from 299 institutions underwent transesophageal echocardiography (TEE) to rule out LA thrombus before ECV. Of these, LA thrombus was found in eight patients (4%), who tended to be older (67.3 vs. 61.3 years, $p=0.175$), had higher $CHADS_2$ scores (1.88 vs. 0.95, $p=0.058$), and a higher prevalence of prior stroke or transient ischemic attack (22.2% vs. 2.6%, $p=0.034$) than those without LA thrombus. Of the eight patients with LA thrombus, one had LA thrombus during a Dabi 150 mg b.i.d treatment, whereas the remaining seven were receiving 110 mg b.i.d for 3 weeks or longer. In 6 of the 8 patients with LA thrombus, a second TEE was performed, revealing complete resolution of LA thrombus in five; among these five patients, one received Dabi dosage of 150 mg b.i.d unchanged, two received an increased dosage from 110 mg to 150 mg b.i.d, and two were switched to warfarin. Two patients had a stroke 3 and 15 days after ECV, and one had a major large intestine bleeding episode during Dabi therapy.
Conclusions: LA thrombus developed in 4% of patients with AF receiving Dabi. Older patients with a higher $CHADS_2$ score receiving a lower Dabi dosage were more likely to develop LA thrombus, which was resolved with a prolonged or increased dosage. A higher Dabi dosage may be more beneficial before ECV but prospective randomized studies would be needed to confirm these results.

1. Introduction

Stroke prevention is of prime importance in the management of patients with atrial fibrillation (AF). Although the risk of thromboembolic stroke is predicted by a variety of factors, including those indicated by the $CHADS_2$ score, electrical cardioversion (ECV) is a special situation where this risk increases temporarily.

Warfarin administration is recommended for at least 3 weeks and 4 weeks before and after elective ECV, respectively, unless the possibility of left atrial (LA) thrombus is excluded by transesophageal echocardiography (TEE) [1–4]. However, the validity of this approach for the use of novel oral anticoagulants (NOACs) is unknown.

Since dabigatran (Dabi) was first introduced in clinical practice on March 14, 2011 in Japan, ECV has been performed during Dabi therapy, providing an opportunity to examine both LA thrombus formation and resolution in patients with AF. Accordingly, the Japanese Heart Rhythm Society (JHRS) conducted a survey of the incidence and the fate of LA thrombus.

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2. Materials and methods

A retrospective questionnaire survey was conducted among 299 JHRS institutions from December 2012 to January 2013. Patients with persistent AF who underwent TEE for elective ECV were included. LA thrombus incidence, risk factors for thrombus formation as indicated by the $CHADS_2$ score, history of gastrointestinal bleeding, Dabi dosage (110 mg b.i.d or 150 mg b.i.d), treatment duration before ECV (<3 weeks, 3–6 weeks, ≥ 6 weeks) and after ECV (<4 weeks, ≥ 4 weeks), and co-administration of amiodarone or verapamil were examined. Patients with LA thrombus underwent repeated TEE to determine LA thrombus fate and the possibility of thrombus resolution. Furthermore, embolic as well as hemorrhagic complications occurring in patients without LA thrombus were evaluated within 1 month of ECV while on Dabi.

Comparisons between patients with and without LA thrombus were made using a Student *t*-test for age and a chi-square test for other variables.

3. Results

3.1. LA thrombus prevalence

A total of 198 patients underwent TEE to rule out the presence of LA thrombus before ECV. The average age was 61.6 years with an 84% male predominance. The average $CHADS_2$ score was 0.99 with 3.5% of patients having a history of stroke or transient ischemic attack.

Dabi 150 mg b.i.d and 110 mg b.i.d were given to 98 and 100 patients, respectively. LA thrombus was found in one patient receiving the higher dosage while seven patients received the lower dosage ($p=0.076$) (Table 1). The decision to administer the lower dosage in 58% of patients was based on Japan's recommendations, which requires the fulfillment of one of the following criteria: creatinine clearance rate, 30–50 mL/min; co-administration of p-glycoprotein inhibitors such as amiodarone or verapamil; age ≥ 70 years; or a history of gastrointestinal bleeding. In the remaining 42% of patients, physicians arbitrarily selected the lower dosage.

Dabi was administered for <3 weeks in 21%, for 3–6 weeks in 24%, and for ≥ 6 weeks in 55% of patients prior to TEE.

Table 1
Characteristics of patients with and without left atrial thrombus. TIA, transient ischemic attack.

	LA thrombus (−)	LA thrombus (+)	Total	*p* Value
n	190	8	198	
Age (yrs; mean ± SD)	61.3 ± 12.0	67.3 ± 12.7	61.6 ± 12.1	$p=0.175$
Male (*n*)	160	7	167	
$CHADS_2$ score (mean)	0.95	1.88	0.99	$p=0.058$
0 or 1 (*n*)	141	3	144	
2 (*n*)	29	4	33	
3–6 (*n*)	14	1	15	
Unknown (*n*)	6	0	6	
Prior stroke/TIA (*n*)	5	2	7	$p=0.034$
150 mg b.i.d	97	1	98	$p=0.076$
110 mg b.i.d	93	7	100	
As recommended*	54	4	58	

* Dose reduction to 110 mg b.i.d according to Japan's recommendations described in the text.

3.2. Characteristics of LA thrombus patients

LA thrombus was found in eight (4%) out of 198 patients (Fig. 1). The eight patients with LA thrombus tended to be older (67.3 vs. 61.3 years, $p=0.175$), had higher $CHADS_2$ scores (1.88 vs. 0.95, $p=0.058$), and had a higher prevalence of prior stroke or transient ischemic attack (22.2% vs. 2.6%, $p=0.034$) than those without LA thrombus (Table 1).

Of the eight patients with LA thrombus, one was receiving a Dabi dosage of 150 mg b.i.d, whereas the remaining seven were receiving 110 mg b.i.d for ≥ 3 weeks. Notably, in three of these seven patients, the dosage of 110 mg b.i.d was arbitrarily selected and did not reflect the Japanese recommendations for dosage reduction as described in Section 3.1.

3.3. LA thrombus fate

A second TEE was performed in six of the eight patients with LA thrombus, which revealed complete resolution of the thrombus in five patients with the earliest resolution within 23 days after the first TEE (Fig. 1). Of these five patients, one was receiving a prolonged Dabi dosage of 150 mg b.i.d, two had an increase in dosage from 110 mg to 150 mg b.i.d, and the remaining two were switched to warfarin (Table 2, Figs. 2 and 3). One patient undergoing the second

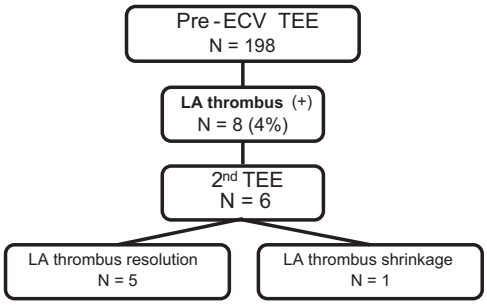

Fig. 1. Summary of serial TEE findings. ECV, electrical cardioversion; TEE, transesophageal echocardiography; LA, left atrial.

Table 2
Characteristics of the eight patients with left atrial thrombus. No, number; Wt, weight; CLcr, creatinine clearance; Dabi, dabigatran; Wks, weeks; TEE, transesophageal echocardiography; OAC, oral anticoagulants.

Patient no.	Age	Sex	Wt (kg)	CLcr (mL/m)	$CHADS_2$ score	Dabi dosage (mg, b.i.d)	Wks of Dabi prior to 1st TEE	2nd OAC for LA thrombus	Days to 2nd TEE	Fate of LA thrombus
1	82	M	68	64	4	110*	3–6	110	–	Unknown
2	63	M	83	77	2	110	≧6	Warfarin	23	Disappeared
3	70	M	52	55	2	110*	≧6	150	58	Disappeared
4	78	M	90	66	2	110*	≧6	Warfarin	–	Unknown
5	82	M	41	42	2	110*	≧6	Warfarin	9	Shrank
6	49	M	96	154	1	110	≧6	150	121	Disappeared
7	58	M	61	89	1	150	≧6	150	308	Disappeared
8	56	F	81	100	1	110	≧6	Warfarin	49	Disappeared

* Dose reduction to 110 mg b.i.d according to Japan's recommendations described in the text.