

Dabigatran Therapy Resulting in the Resolution of Rivaroxaban-resistant Left Atrial Appendage Thrombi in Patients with Atrial Fibrillation

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Abstract

Patients with persistent atrial fibrillation (AF) and a large left atrium are at a high risk for thromboembolisms. Recently, direct oral anticoagulants (DOACs) have mainly been used for the prevention of cardiac embolisms caused by AF. Transesophageal echocardiography (TEE) is performed in order to exclude any left atrial appendage (LAA) thrombi. We herein report two cases of persistent AF, both of which were treated with rivaroxaban for more than two years. Since TEE identified mobile LAA thrombi with this treatment, we switched from rivaroxaban to the direct thrombin inhibitor dabigatran. Dabigatran resolved the LAA thrombi that had been refractory to rivaroxaban.

Key words: atrial fibrillation, thromboembolism, direct oral anticoagulants

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Introduction

Atrial fibrillation (AF) is a common cause of cerebral infarctions and systemic embolization (1, 2). Warfarin is an established anticoagulation therapy for reducing the risk of stroke in patients with AF by preventing thrombus formation (3). Direct oral anticoagulants (DOACs) have been established as being safer and more effective than warfarin for the prophylaxis of thromboembolisms in patients with non-valvular AF (4-7). However, whether or not the direct thrombin inhibitor (DTI) dabigatran has thrombolytic action against pre-existing factor Xa inhibitor-resistant intracardiac thrombi is unclear. In this report, we described two cases of rivaroxaban-resistant left atrial thrombi that were dissolved after initiating dabigatran therapy.

Case Reports

Case 1

A 67-year-old man with long persistent AF was treated

with rivaroxaban 15 mg daily (creatinine clearance 72 mL/min) for 3 years. Regarding his medical history, he had arterial hypertension and hyperuricemia, and had received gastric cancer surgery at 62 years of age. He had no family history of cardiovascular disease or thrombotic disease. Anticoagulation with rivaroxaban was indicated with a CHADS₂ score of 1 and CHADS₂VASc score of 2. Transthoracic echocardiogram performed before admission revealed a left ventricular end-diastolic dimension of 50 mm, ejection fraction of 61%, and left atrial dimension of 52 mm. As the AF was symptomatic and refractory to medication, catheter ablation was planned. Transesophageal echocardiography (TEE) identified a mobile left atrial appendage (LAA) thrombus (10 mm×14 mm) despite approximately 3 years of anticoagulation therapy using rivaroxaban with good adherence (Fig. 1A). Therefore, rivaroxaban was switched to the DTI dabigatran (300 mg daily). Six weeks later, TEE revealed the resolution of the LAA thrombus (Fig. 1B). There was no marked difference in the D-dimer level before and after treatment with dabigatran (0.80 µg/mL each time). Pulmonary vein isolation was performed without any complications. Since then, the patient has remained in sinus rhythm.

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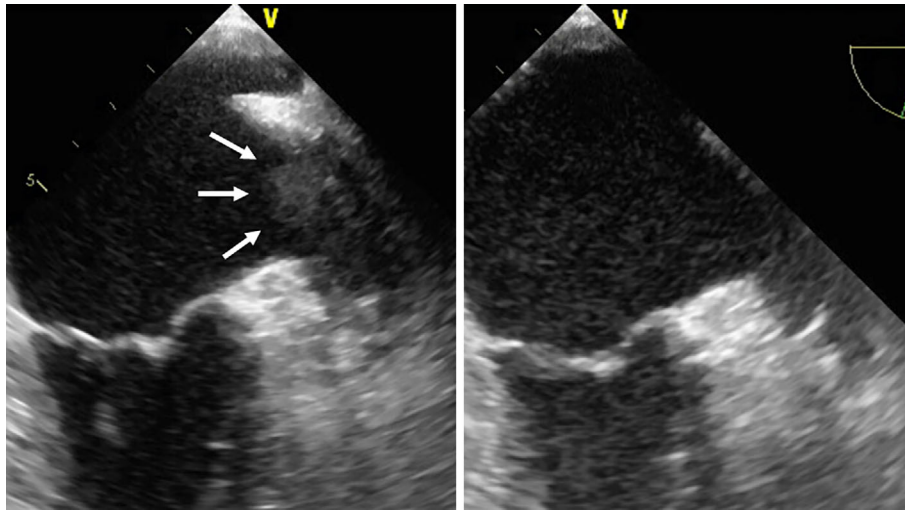


Figure 1. (A) Transesophageal echo shows mobile thrombus in the left atrial appendage (LAA, arrow). (B) Transesophageal echo shows resolution of the LAA thrombus after six weeks' anticoagulation with dabigatran.

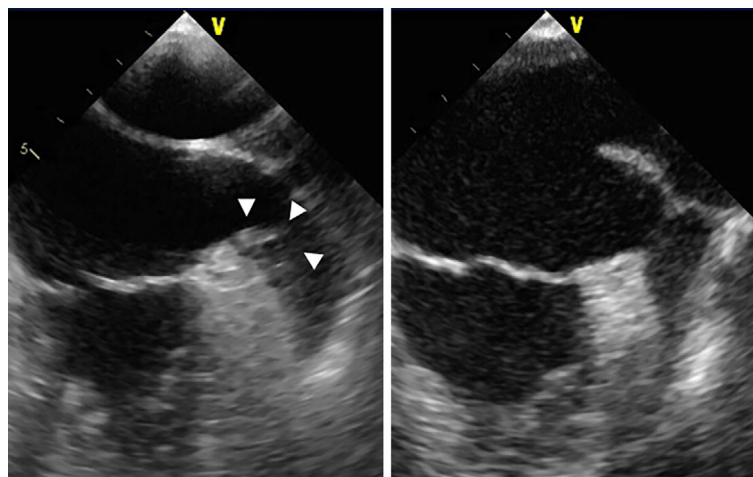


Figure 2. (A) Transesophageal echo shows mobile thrombus in the left atrial appendage (LAA, arrowhead). (B) Transesophageal echo shows resolution of the LAA thrombus after 12 months' anticoagulation with dabigatran.

Case 2

A 74-year-old man with long persistent AF was treated with rivaroxaban 15 mg daily (creatinine clearance 53 mL/min) for 2 years. Regarding his medical history, he had arterial hypertension and diabetes mellitus. He had no family history of cardiovascular disease or thrombotic disease. Anticoagulation with rivaroxaban was indicated with a CHADS2 score of 2 and CHADS2-VASc score of 3. Transthoracic echocardiogram performed before admission revealed a left ventricular end-diastolic dimension of 52 mm, ejection fraction of 64%, and left atrial dimension of 51 mm. As the atrial fibrillation was symptomatic and refractory to medication, catheter ablation was planned. TEE identified a mobile LAA thrombus (5 mm×10 mm) despite approximately 2 years of anticoagulation therapy using rivaroxaban with good adherence (Fig. 2A). The D-dimer level was 0.80 µg/

mL. Therefore, rivaroxaban was switched to the DTI dabigatran (300 mg daily). Twelve months later, TEE revealed the resolution of the LAA thrombus (Fig. 2B). The D-dimer level was 0.40 µg/mL at that time.

No thromboembolisms occurred between the initiation of dabigatran and the thrombus resolution in either of these two cases.

Discussion

Left atrial thrombi are present in approximately 4-27% of patients with AF, regardless of their clinical type (paroxysmal, persistent, and permanent) (8-12). In this report, we described two cases of patients with rivaroxaban-resistant left atrial thrombi that dissolved after initiating dabigatran. To our knowledge, this is the first report to demonstrate the efficacy of dabigatran in resolving pre-existing intracardiac

thrombi refractory to the factor Xa inhibitor rivaroxaban.

DOACs have been shown to be as safe and effective for the treatment of non-valvular AF as conventional vitamin K antagonists (4, 5). Among the available DOACs, dabigatran is the only oral anticoagulant that functions as a DTI and pro-drug, while the others (rivaroxaban, apixaban, and edoxaban) function as factor Xa inhibitors in their active form.

A previous study reported that a larger left atrial dimension, lower left ventricular ejection fraction, left atrial spontaneous echo, and left ventricular hypertrophy were associated with left atrial thrombi formation (13, 14). In our report, both cases had long-persistent AF and large left atrial dimensions.

Warfarin acts by inhibiting the hepatic synthesis of vitamin K-dependent coagulation factors (15). In contrast, DTIs such as dabigatran seem to obstruct tenase by inhibiting thrombin generated in the initiation phase as well as preventing feedback to the amplification phase of cell-based coagulation reactions. During blood clotting, the heparin-antithrombin complex cannot bind fibrin-bound thrombin. However, given their mechanism of action, DTIs can bind to and inhibit the activity of not only soluble thrombin but also fibrin-bound thrombin. Since DTIs reduce the thrombin-mediated activation of platelets, they also have an antiplatelet effect (16). The thrombin production is completely obstructed in the blood concentration peak. Such effects are not achieved with factor Xa inhibitors. Since dabigatran can inhibit thrombus development and fibrin formation, dabigatran administration is more effective in reducing a left atrial spontaneous echo contrast than warfarin (14). It is also extremely effective in directly inhibiting thrombin, as it can absolutely control any excessive thrombin production that might cause morbid clot formation.

In contrast to dabigatran, factor Xa inhibitors are considered to inhibit the activity of factor Xa mainly in the prothrombinase complex of the propagation phase (17). These drugs vary in regard to their bioavailability, renal excretion rate, and liver metabolism; however, the plasma elimination half-life of rivaroxaban is shorter than that of dabigatran (dabigatran 12-17 hours, rivaroxaban 5-9 hours) (18). These inhibitors can be delivered in regimens of once (rivaroxaban, edoxaban) or twice (dabigatran, apixaban) a day.

As a result, it may thus be possible to use DOACs as a once-daily regimen in which the anticoagulant effect disappears at the trough phase, although the risk of thrombosis formation is higher at this point than at the peak phase. Since rivaroxaban is administered as a once-daily regimen, there is a larger difference between the peak and trough levels than with twice-daily regimens. At the trough level, the hemostatic activity is nearly normal, as most of the effect of the administered DOAC has disappeared by this point. With intermittent anticoagulation, the risk of thrombus formation during the period of no anticoagulation around the trough should be considered. While DOACs seem to have no marked difference in thrombosis prevention effect, dabiga-

tran may be superior to rivaroxaban with respect to its dissolution effect on pre-existing clots.

We concluded that the DTI dabigatran administered twice a day was effective in resolving pre-existing thrombi and would be more effective in reducing any thrombus formation than a factor Xa inhibitor administered once a day.

The authors state that they have no Conflict of Interest (COI).

References

- Hart RG, Coull BM, Hart D. Early recurrent embolism associated with nonvalvular atrial fibrillation: a retrospective study. *Stroke* **14**: 688-693, 1983.
- Atrial fibrillation: current understandings and research imperatives. The National Heart, Lung, and Blood Institute Working Group on Atrial Fibrillation. *J Am Coll Cardiol* **22**: 1830-1834, 1993.
- Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet* **343**: 687-691, 1994.
- Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* **361**: 1139-1151, 2009.
- Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* **365**: 883-891, 2011.
- Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **365**: 981-992, 2011.
- Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* **369**: 2093-2104, 2013.
- Ellis K, Ziada KM, Vivekananthan D, et al. Transthoracic echocardiographic predictors of left atrial appendage thrombus. *Am J Cardiol* **97**: 421-425, 2006.
- Leung DY, Davidson PM, Cranney GB, Walsh WF. Thromboembolic risks of left atrial thrombus detected by transesophageal echocardiogram. *Am J Cardiol* **79**: 626-629, 1997.
- Tsai LM, Lin LJ, Teng JK, Chen JH. Prevalence and clinical significance of left atrial thrombus in nonrheumatic atrial fibrillation. *Int J Cardiol* **58**: 163-169, 1997.
- Stoddard MF, Singh P, Dawn B, Longaker RA. Left atrial thrombus predicts transient ischemic attack in patients with atrial fibrillation. *Am Heart J* **145**: 676-682, 2003.
- Thambidorai SK, Murray RD, Parakh K, et al. Utility of transesophageal echocardiography in identification of thrombogenic milieu in patients with atrial fibrillation (an ACUTE ancillary study). *Am J Cardiol* **96**: 935-941, 2005.
- Kimura M, Wasaki Y, Ogawa H, et al. Effect of low-intensity warfarin therapy on left atrial thrombus resolution in patients with nonvalvular atrial fibrillation: a transesophageal echocardiographic study. *Jpn Circ J* **65**: 271-274, 2001.
- Watanabe T, Shinoda Y, Ikeoka K, et al. Dabigatran exhibits low intensity of left atrial spontaneous echo contrast in patients with nonvalvular atrial fibrillation as compared with warfarin. *Heart Vessels* 2016 (Epub ahead of print).
- Corrado G, Tadeo G, Beretta S, et al. Atrial thrombi resolution after prolonged anticoagulation in patients with atrial fibrillation. *Chest* **115**: 140-143, 1999.
- Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. *N Engl J Med* **353**: 1028-1040, 2005.
- Ieko M, Naitoh S, Yoshida M, Takahashi N. Profiles of direct oral anticoagulants and clinical usage-dosage and dose regimen differences. *J Intensive Care* **4**: 19, 2016.

18. Galanis T, Keiffer G, Merli G. The new oral anticoagulants for the treatment of venous thromboembolism: a new paradigm shift in antithrombotic therapy. *Curr Ther Res Clin Exp* **76**: 76-83, 2014.

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