

Thromboembolic Events in Patients with Hypertrophic Cardiomyopathy and Atrial Fibrillation During New Oral Anticoagulant Therapy

INTRODUCTION

All patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF) should receive anticoagulants owing to their high thromboembolic risk. Despite the absence of dedicated randomized controlled studies, limited observational studies have suggested that new oral anticoagulants (NOACs) may be effective and safe in patients with HCM and AF.^{1,2} Here, we report 2 cases of thromboembolic events within 6 months of switching anticoagulation from a vitamin K antagonist (warfarin) to an NOAC in patients with HCM and AF.

CASE REPORTS

Case 1

A 53-year-old man with septal HCM and persistent AF presented to the emergency department with altered mental status. He underwent implantation of a pacemaker due to a complete atrioventricular block 22 years earlier. He had a cerebrovascular attack 9 years previously, and persistent AF was later diagnosed. His CHA₂DS₂-VASc score was 3 (congestive heart failure and history of stroke). He had been prescribed oral anticoagulant therapy with warfarin, and neither thromboembolic nor bleeding events were reported during 5 years of warfarin therapy. He received an evaluation of the international normalized ratio (INR) and adjustment of dosage for targeting an INR of 2.0-2.5 at intervals of 2-3 months. Time in a therapeutic range over the past 3 years was 76.5%. Six months prior to visiting the emergency room, warfarin was switched to a direct thrombin inhibitor, dabigatran (150 mg b.i.d.), based on the patient's preference. The adherence to dabigatran was excellent, which was confirmed in the outpatient visit at intervals of 3 months, and administration of dabigatran was confirmed at a healthcare center every day. Computed tomography (CT) angiography revealed a new occlusion at the distal M1 segment of the right middle cerebral artery (Figure 1A). Echocardiography revealed end-stage HCM with severely reduced left ventricular ejection fraction (LVEF, 34%) and left atrial enlargement (Figure 1B and Supplementary Video 1). The patient's poor condition precluded a return to warfarin therapy; thus, the anticoagulant therapy was switched to apixaban (5 mg b.i.d.) at the discretion of the neurologist, and the patient was discharged. The patient died 5 months later because of an aggravated general condition and aspiration pneumonia.

Case 2

A 42-year-old man with apical HCM and persistent AF presented to the emergency department with abdominal pain. He underwent implantation of an implantable cardioverter defibrillator due to documented ventricular fibrillation 13 years earlier. Over the previous 18 years, he underwent regular follow-ups at the cardiology department for HCM and persistent AF. He experienced renal infarction 12 years previously and had been prescribed warfarin thereafter. The patient's CHA₂DS₂-VASc score was 4 (congestive heart failure, hypertension, and history of systemic embolism). During 12 years of warfarin therapy, neither thromboembolic nor

CASE REPORT



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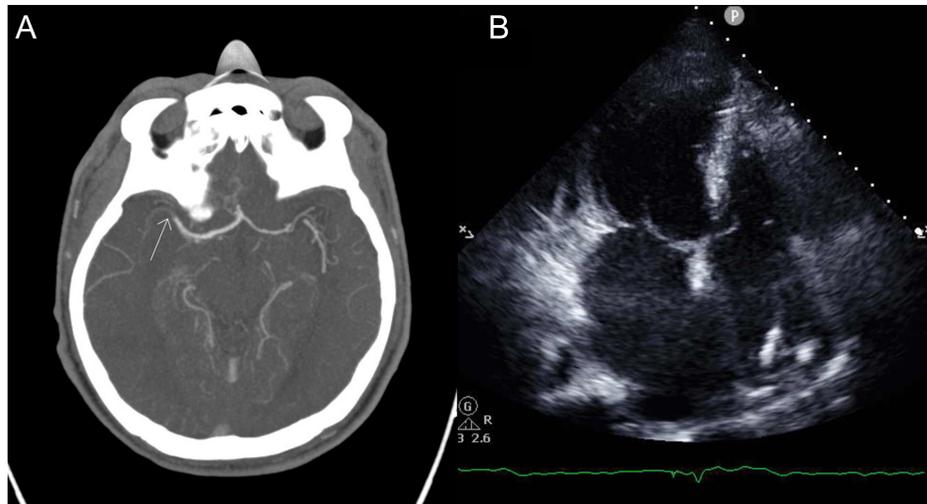


Figure 1. (A) Brain CT angiography reveals occlusion at the distal M1 segment (white arrow) of the right middle cerebral artery. (B) Echocardiography shows a severely reduced LVEF (34%) with resolution of left ventricular hypertrophy suggesting end-stage HCM and left atrial enlargement. CT, computed tomography; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction.

bleeding events were reported. He received an evaluation of INR and adjustment of dosage for targeting an INR of 2.0-2.5 at intervals of 2-3 months. Time in a therapeutic range over the past 3 years was 89.7%. Five months before visiting the emergency room, warfarin was switched to a direct thrombin inhibitor, dabigatran (150 mg b.i.d.) based on the patient's preference. The adherence to dabigatran was excellent, which was confirmed in every outpatient visit, and administration of dabigatran was confirmed by his family member every day. Abdominopelvic CT revealed multifocal right renal and splenic infarctions (Figure 2A). Echocardiography revealed apical hypertrophy of the left ventricle with a normal LVEF (62%) and left atrial enlargement (Figure 2B and Supplementary Video 2). Thrombolysis was performed for the right renal infarction, and dabigatran was switched back to warfarin therapy, targeting INR levels from 2.0 to 3.0. No

thromboembolic or bleeding events were reported during warfarin therapy over the next 24 months.

DISCUSSION

Atrial fibrillation is commonly observed in HCM patients, markedly increasing the incidence of thromboembolism and morbidity.^{3,4} Anticoagulant therapy with warfarin was associated with a 54.8% relative risk reduction of thromboembolism in patients with HCM and AF.⁵ Oral anticoagulation is beneficial for stroke reduction, and the guideline recommends that all patients in these demographics receive anticoagulation.⁶

However, no anticoagulation regimens for patients with HCM and AF have been established. New oral anticoagulants have shown an improved efficacy/safety ratio and are considered

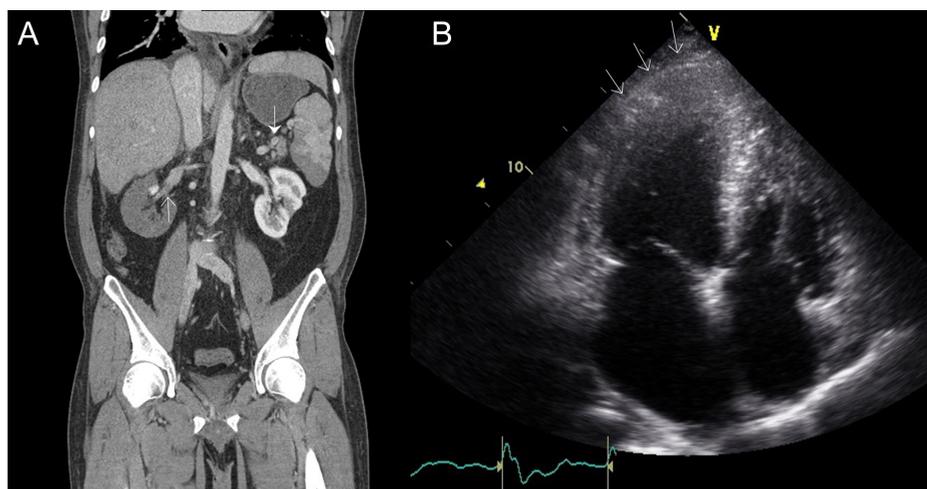


Figure 2. (A) Abdominopelvic CT reveals decreased enhancement of the right kidney and spleen with decreased enhancement of the right renal artery (white arrow) and splenic vein (white arrowhead), suggestive of multifocal right renal and splenic infarction due to thrombus. (B) Echocardiography reveals apical hypertrophy of the left ventricle (white arrows) with normal LVEF and left atrial enlargement. CT, computed tomography; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction.

the preferred choice of anticoagulants to prevent stroke in the general AF population according to worldwide AF guidelines.⁶ However, few patients with HCM were included in previous NOAC trials, precluding subgroup analysis, and the systematic data regarding the efficacy and safety of NOACs in patients with HCM and AF are limited. Only a few observational studies using real-world data have suggested that both warfarin and NOACs are safe and effective in reducing thromboembolic risk.

Observational datasets of 2198 patients with HCM and AF treated with anticoagulants from a United States commercial insurance database demonstrated that the rates of embolic ischemic stroke and bleeding were similar between warfarin and NOAC therapies over a short-term follow-up period.¹ However, the follow-up duration was too short (average of 0.56 years); clinical characteristics such as mitral valve dysfunction, left atrial enlargement, and left ventricular dysfunction that may predispose the patients to cardioembolism were lacking, and the presence of thromboembolism history was not mentioned.

Observational studies including 2397 patients with HCM and AF treated with anticoagulants who were enrolled in a nationwide Korean database showed that the rates of embolic ischemic stroke and bleeding complications were significantly lower in patients treated with NOACs than in those treated with warfarin.² However, the purpose of this study was to evaluate the efficacy of NOACs as a primary prevention for stroke. Patients with a history of ischemic stroke or systemic embolism, intracranial hemorrhage, or gastrointestinal bleeding were excluded, making the study inappropriate to evaluate the safety and efficacy in high-risk patients with a history of thromboembolic events and possibly underestimate the thromboembolic incidence of NOAC therapy. Patients consuming NOACs also had shorter follow-up duration than those consuming warfarin (1.0 ± 0.8 vs. 2.4 ± 1.7 years, respectively), which may cause an underestimation of the thromboembolic incidence in NOAC therapy.

CONCLUSION

In our study, 2 patients who showed a stable condition during warfarin therapy experienced thromboembolic events within 6 months after their medication was switched to an NOAC. Although recent observational data have demonstrated the efficacy of NOACs in preventing thromboembolic events in patients with HCM and AF, they should be used cautiously. In light of these 2 case reports, warfarin needs to be reconsidered for the secondary prevention of thromboembolic

events in patients with HCM and AF. Prospective randomized studies are warranted to evaluate the safety and efficacy of warfarin compared with NOACs for the secondary prevention of thromboembolic events in the setting of HCM and coexistent AF.

Informed Consent: Written informed consent was obtained from the patients for the publication of the case report and accompanying images.

Declaration of Interests: The authors have no conflict of interest to declare.

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Supplementary Video 1: Echocardiography shows severely reduced LVEF (34%) with resolution of left ventricular hypertrophy, suggesting end-stage HCM and left atrial enlargement. HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction.

Supplementary Video 2: Echocardiography reveals apical hypertrophy of the left ventricle with normal LVEF (62%) and left atrial enlargement. HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction.

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