Optimal nonvitamin K antagonist oral anticoagulant therapy in a warfarin-sensitive patient after left atrial appendage closure

A case report

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Abstract

Rationale: Developing an optimal medication strategy poses a challenging task in fragile patients after left atrial appendage closure (LAAC). We report an optimal nonvitamin K antagonist oral anticoagulant (NOAC) therapy in a warfarin-sensitive patient after LAAC.

Patient concerns: A 77-year-old nonvalvular atrial fibrillation (NVAF) male carrying 2 warfarin-sensitive alleles experienced 2 gum-bleeding with the international normalized ratio (INR) around 3.

Diagnoses: Persistent NVAF with a history of subtotal gastrectomy and moderate renal insufficiency.

Interventions: Warfarin was discontinued and vitamin K1 was immediately administrated via intravenous infusion. LAAC was regarded as a preferable option, and rivaroxaban 15 mg daily was managed after LACC.

Outcomes: Complete endothelialization on the surface of device was detected via transoesophageal echocardiography (TEE), and no peridevice spillage and adverse event occurred.

Lessons: A post-LAAC treatment with NOAC may be a viable regimen in patients intolerant to warfarin.

Abbreviations: DAPT = dual antiplatelet therapy, INR = international normalized ratio, LAA = left atrial appendage, LAAC = left atrial appendage closure, NOAC = nonvitamin K antagonist, NVAF = nonvalvar atrial fibrillation, OAC = oral anticoagulation, SSE = stroke or systemic embolism, TEE = transoesophageal echocardiography.

Keywords: anticoagulant, atrial fibrillation, left atrial appendage closure, nonvitamin K antagonists, rivaroxaban

1. Introduction

Patients with nonvalvular atrial fibrillation (NVAF) are at increased risk of thrombosis, and left atrial appendage (LAA) is considered as an approximate 90% source of thromboembolism.\textsuperscript{[1]} Oral anticoagulation (OAC) is a standard therapy for preventing stroke or systemic embolism (SSE). Whereas, LAA closure (LAAC) may represent a preferable alternative in patients who are at high risk of SSE as well as clear contraindications for OAC (class IIb, level of evidence C).\textsuperscript{[2]} After successful LAAC, short-term OAC is of great significance to prevent on-device thrombus formation without increasing the risk of bleeding complication.\textsuperscript{[3]} At present, post-LAAC medical strategies recommended by consensus include a combination of warfarin and aspirin for at least 6 weeks, followed by 6 months dual antiplatelet therapy (DAPT) with clopidogrel and lifelong management of aspirin.\textsuperscript{[3]} Nevertheless, owing to inter- and intrapatient variability, warfarin appears to be unsuitable for patients with poor time in therapeutic range and high risk of bleeding. Thus, developing the optimal medication strategy poses a challenging task in these fragile patients. Although the role of nonvitamin K antagonists (NOACs) remains undefined after LAAC, rivaroxaban was chosen as a favorite in consideration of available evidence and patient’s characteristic. At 2 months follow-up, transoesophageal echocardiography (TEE) result supported our choice.

2. Case report

Approval for the study by the local institution review board was not required because it was a case report. The patient provided a written informed consent. A 77-year-old persistent NVAF male (weight of 50 kg) with a history of subtotal gastrectomy and moderate renal insufficiency (creatinine clearance rate of 45 mL/minute), who had been taking warfarin with the dosage of 1.25 mg daily for 3 weeks, suffered from a moderate gum bleeding at the presence of international normalized ratio (INR)
LAAC is a nonpharmacologic alternative for SSE prevention in patients with NVAF, which is recommended by current clinical practice guidelines. Originally, enthusiasm for LAAC was dampened by an unexpected high incidence of periprocedural complications. In the early stage following the LAAC, clots may form on the surface of device, and thus preventive strategy should be applied until complete device endothelialization on device. However, uncertainty remains on the focus of optimal postprocedural drug regimen and duration of treatment. Currently accepted drug strategy comes mainly from 2 randomized clinical trials comparing LAAC with vitamin K antagonist, namely, PROTECT AF and PREVAIL. Of which, patients were taken a coadministration of aspirin 75 mg and clopidogrel 75 mg for 6 months, and lifelong management of aspirin 75 mg. Based on the above-mentioned strategy, 3.4% of patients occurred a device-surface thrombus during TEE evaluation at 45 days post-LAAC.

It is of note that warfarin dose have significant ethnic difference due to alleles of VKORC1 and CYP2C9. VKORC1 (rs9923231) was a common single-nucleotide polymorphism (SNP) in VKORC1, leading to a protein product with no enzyme activity. The mutation frequency of VKORC1 (rs9923231) is about 40% in Caucasians and 10% in Africans, but affects up to near 95% in Asians. Unlike VKORC1 (rs9923231), the mutation rate of CYP2C9*3 was only 2% to 5% in Asians. In the present case, the reduced-function allele carrier of both VKORC1 and CYP2C9 induced a relatively low dosage of warfarin. In addition, elderly person and low weight (50 kg) were also factors that led to low warfarin dose. Therefore, the predicted dose of warfarin was 1.3 mg/daily by using a web application (www.warfarindosing.org) that involved clinical variables and also SNPs in VKORC1 and CYP2C9, which was line with the actual warfarin dosage in the present patient. It is also noteworthy that the patient experienced continuous gum bleeding at the presence of INR around 3. Collectively, he was considered as a warfarin-sensitive patient, and hard to reach satisfying INR control.

Other optimal antithrombotic therapy should be considered in such fragile patients. In the PLAATO study, patients were treated with DAPT consisting of aspirin and clopidogrel for 4 to 6 weeks after LAAC, and no device-surface thrombus occurred during TEE follow-up. Thus, short-term drug regimen with DAPT appears to be a reasonable option in patients intolerant to warfarin. Whereas, in a recent EWOLUTION study, those prescribed DAPT after WATCHMAN implantation showed a numerically highest rate of device-associated thrombus when compared to warfarin (3.1% vs 0.8%). Interestingly, patients on NOACs had the numerically lowest rate of thrombus information on device as well as major bleeding in comparison to DAPT (1.3% vs 3.1% for device-associated thrombus; 1.9% vs 2.4% for major bleeding). On the basis of above-mentioned data, NOACs are likely to come with a good balance between device-related thrombus and bleeding in high risk patients. Several reasons needed to be considered with regard to an optimal choice of NOACs: only dabigatran and rivaroxaban are available in China; the patient had a history of subtotal gastrectomy, and the use of dabigatran may increase the risk of gastrointestinal bleeding; rivaroxaban depend on lesser degree on renal excretion compared to dabigatran (36% vs 80%), and the patient had a moderate renal insufficiency with Ccr of 45 mL/minute; and reduced dosage of rivaroxaban 15 mg daily is recommended based on the results of ROCKET-AF and J-ROCKET AF. Summarily, rivaroxaban 15 mg daily represents a preferable choice. The patient had been doing well without device-related thrombus and bleeding at 2 months follow-up.

Based on the clinical setting of this case and current evidence, NOACs may represent a reasonable alternative regarding the
inhibition of device-associated thrombus and bleeding in patients intolerant to warfarin. In addition, further studies on evaluation of the optimal drug strategy in LAAC patients are necessary.

4. Conclusion
A post-LAAC treatment with NOACs may be a viable regimen in patients intolerant to warfarin. Whereas, further design of randomized clinical trials as well as real-world studies on evaluation of NOACs in LAAC patients are necessary.

Author contributions
Long Shen and Zhi-Chun Gu was involved in the care of the patient and wrote the manuscript; Sha-Sha Fang was responsible for collecting the patient’s information; Heng Ge was responsible for the treatment of patient; Zhi-Qing Qiao performed the patient’s transesophageal echocardiography. All authors read and approve the manuscript.

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