Clinical Case Report

Medicine®

OPEN

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

A case report

Long Shen, MD[a], Sha-Sha Fang, MD[b], Heng Ge, MD, PhD[a], Zhi-Qing Qiao, MD[a], Zhi-Chun Gu, MD[c,*]

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 = nonvalvular 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.[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).[2] After successful LAAC, short-term OAC is of great significance to prevent on-device thrombus formation without increasing the risk of bleeding complication.[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.[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)

Editor: N/A.

LS, S-SF, and HG contributed equally as first coauthors.

Funding/support: This work was supported by the Science Fund of Hospital Pharmacy of Shanghai Jiaotong University School of Medicine (JDYX2016ZD003), Program for Key Discipline of Clinical Pharmacy of Shanghai (2016-40044-002), and Program for Key but Weak Discipline of Shanghai Municipal Commission of Health and Family Planning (2016ZB0304).

The authors have no conflicts of interest to disclose.

[a] Department of Cardiology, Renji Hospital, School of Medicine, Shanghai Jiaotong University, [b] Department of Pharmacy, Third Affiliated Hospital of Second Military Medical University, [c] Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China.

[*] Correspondence: Zhi-Chun Gu, Department of Pharmacy, Renji Hospital, School of Medicine, Shanghai Jiaotong University, Pujian Road 160, Shanghai 200127, China (e-mail: guzhichun213@163.com).

Medicine (2018) 97:18(e0683)

Received: 30 January 2018 / Accepted: 17 April 2018

http://dx.doi.org/10.1097/MD.0000000000010683

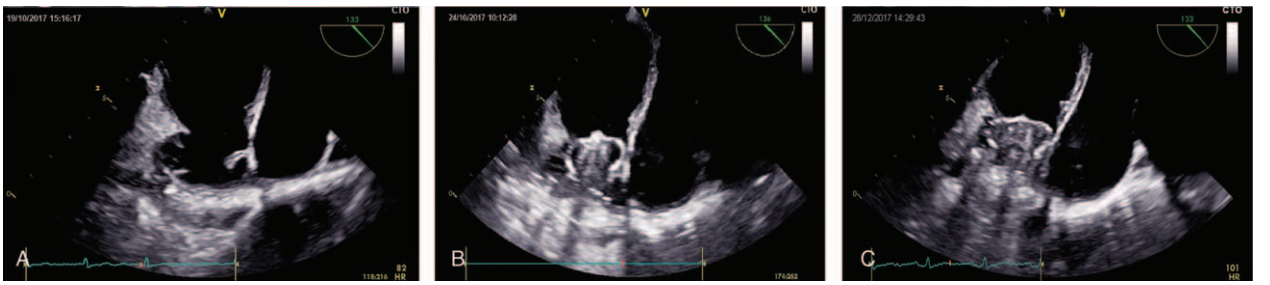

Figure 1. (A) Transoesophageal echocardiography result before LAAC; (B) no on-device thrombus formation at the time of LACC; and (C) no on-device thrombus formation at 2 months follows after LACC.

being 3.41 outside the hospital. The patient's gum bleeding was well controlled after the discontinuity of warfarin. After admission, warfarin at the dosage of 1.25 mg daily was given again for the prevention of SSE. Similar to last time, the patient undergone serious gum hemorrhage with the INR of 3.05. At this juncture, warfarin was discontinued and vitamin K1 5 mg was immediately administrated via intravenous infusion. About 1 hour later, the patient's gum bleeding improved, and INR value returned to 2.07. The genetic testing for warfarin showed that the patient carries reduced-function alleles of VKORC1 (AA) and CYP2C9 (*1/*3). Thus, he was considered as a warfarin-sensitive gene carrier and less likely to do well on warfarin. Meanwhile, when regarding a high risk of stroke (CHA_2DS_2-VASc score of 2) and intolerance to OAC of the present patient, LAAC was regarded as a preferable option on the basis of patient's aspiration. Afterward, a 12 mm WATCHMAN device (Boston Scientific) was successful implanted into LAA without spillage around device, and radiofrequency ablation was performed at the same time (Fig. 1A, B). Inevitably, post-LAAC OAC was necessary until complete device endothelialization. Finally, rivaroxaban at the sustained dosage of 15 mg daily was managed after comprehensive discussion with the clinical pharmacist. After bimestrial usage of rivaroxaban 15 mg daily, complete endothelialization on the surface of device was detected via TEE, and no peridevice spillage and adverse event occurred during follow-up (Fig. 1C).

3. Discussion

LAAC is a nonpharmacologic alternative for SSE prevention in patients with NVAF, which is recommended by current clinical practice guidelines.[2] Originally, enthusiasm for LAAC was dampened by an unexpected high incidence of periprocedural complications.[4] In the early stage following the LAAC, clots may form on the surface of device, and thus preventive strategy should be applied until complete 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.[4–6] Of which, patients were taken a coadministration of warfarin plus aspirin 75 mg for 45 days, followed by the combination 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.[5,6]

It is of note that warfarin dose have significant ethnic difference due to alleles of VKORC1 and CYP2C9.[7] VKORC1 (rs9923231) was a common single-nucleotide polymorphism (SNP) in VKORC1, leading to a protein product with no enzyme activity.[8] The mutation frequency of VKORC1 (rs9923231) is about 40% in Caucasians and 10% in Africans, but affects up to near 95% in Asians.[8] Unlike VKORC1 (rs9923231), the mutation rate of CYP2C9*3 was only 2% to 5% in Asians.[9] 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 leaded to low warfarin dose.[10] 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.[10] 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.[11] 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%).[12] 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).[12] 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[13]; 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[14]; and reduced dosage of rivaroxaban 15 mg daily is recommended based on the results of ROCKET-AF and J-ROCKET AF.[15,16] 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.

Data curation: Zhiqing Qiao.

Writing – original draft: Long Shen, Shasha Fang, Heng Ge, Zhichun Gu.

References

[1] Beigel R, Wunderlich NC, Ho SY, et al. The left atrial appendage: anatomy, function, and noninvasive evaluation. JACC Cardiovasc Imaging 2014;7:1251–65.

[2] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78.

[3] Schmidt B, Chun KR. Antithrombotic therapy after left atrial appendage closure. Expert Rev Cardiovasc Ther 2015;13:105–9.

[4] Holmes DR, Reddy VY, Turi ZG, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009;374:534–42.

[5] Reddy VY, Holmes D, Doshi SK, et al. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011;123: 417–24.

[6] Holmes DRJr, Kar S, Price MJ, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol 2014;64:1–2.

[7] De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease. Thromb Haemost 2013;110: 1087–107.

[8] Askari B, Khaleqsefat E, Khalafkhani D, et al. Study on a novel polymorphism in the VKORC1 promoter region using bioinformatic tools and warfarin dosing data. Thromb Res 2017;158:76–8.

[9] Gage BF, Bass AR, Lin H, et al. Effect of genotype-guided warfarin dosing on clinical events and anticoagulation control among patients undergoing hip or knee arthroplasty: The GIFT Randomized Clinical Trial. JAMA 2017;318:1115–24.

[10] International Warfarin Pharmacogenetics Consortium , Klein TE, Altman RB, et al. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009;360:753–64.

[11] Block PC, Burstein S, Casale PN, et al. Percutaneous left atrial appendage occlusion for patients in atrial fibrillation suboptimal for warfarin therapy: 5-year results of the PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) Study. JACC Cardiovasc Interv 2009;2:594–600.

[12] Bergmann MW, Betts TR, Sievert H, et al. Safety and efficacy of early anticoagulation drug regimens after WATCHMAN left atrial appendage closure: three-month data from the EWOLUTION prospective, multi-centre, monitored international WATCHMAN LAA closure registry. EuroIntervention 2017;13:877–84.

[13] Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 2017;359:j5058.

[14] Pelliccia F, Rosanio S, Marazzi G, et al. Efficacy and safety of novel anticoagulants versus vitamin K antagonists in patients with mild and moderate to severe renal insufficiency: focus on apixaban. Int J Cardiol 2016;225:77–81.

[15] Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J 2011;32:2387–94.

[16] Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study. Circ J 2012;76:2104–11.