Srce i krvni sudovi 2017; 36(S2): 59-61

Case Report

Oral anticoagulant therapy for stroke prevention in patients with atrial fibrillation and recent major bleeding event

Tatjana S. Potpara[1,2], Milan Nedeljkovic[1,2], Zlatiborka Mijatovic[2]

[1]School of Medicine, Belgrade University, Belgrade, Serbia; [2]Cardiology Clinic, Clinical Centre of Serbia, Belgrade, Serbia.

A 76-year old female patient was referred to our hospital for consultation regarding further treatment for permanent atrial fibrillation (AF) of unknown duration, accidentally detected 2.5 years ago at a routine follow-up visit for her hypertension. Upon the documentation of AF, the patient was prescribed a vitamin K antagonist (VKA) warfarin.

The patient reported a history of hypertension, diabetes mellitus, rheumatoid arthritis, cigarette smoking and recent hospitalization for gastrointestinal bleeding. Her medical records also revealed a mild-to-moderate chronic kidney disease with a creatinine clearance (CrCl) of 48mL/min and labile International Normalized Ration (INR) values, ranging from 1.4 up to 4.5. Five weeks ago, she was discharged from local hospital where she was treated for a major upper gastrointestinal bleeding with transient drop in haemoglobin value from 125g/l to 92g/l. Endoscopic gastrointestinal tract examination performed at admission to the local hospital revealed a diffuse erosive gastritis with multiple gastric mucosal erosions, two small ulcerations and active bleeding. Her INR at admission was 4.2. The patient was treated with gastroprotective therapy (a proton pump inhibitor) and received a transfusion (two doses of packed red cells). Warfarin was discontinued. Several weeks before the bleeding event, the patient experienced an exacerbation of her rheumatoid arthritis and started with regular daily intake of a non-steroidal anti-inflammatory drug until the admission to hospital

At discharge, the patient was prescribed most of her pre-admission medication (that is, a beta-blocker, angiotensin converting enzyme inhibitor (ACEi), dihydropyridine calcium channel blocker, thiazide diuretic, proton pump inhibitor and oral antidiabetic drug), but not oral anticoagulant therapy.

On admission to our hospital, the patient had no particular complaints. Physical examination revealed normal finding, except for the irregular heart rhythm. Heart rate was 82bpm, systolic blood pressure was 140mmHg and diastolic blood pressure was 80mmHg. Electrocardiographic recording revealed atrial fibrillation with ventricular rate of 80bpm. Blood testing showed a haemoglobin value of 121g/l and slightly elevated serum creatinine (CrCl was 50mL/min), whilst other blood tests were within normal limits, including her blood glucose level and HBA1c (5.6%). Transthoracic echocardiographic examination revealed a dilated left atrium (51mm) with moderate functional mitral regurgitation, normal left ventricular end-diastolic and end-systolic diameters (50 and 36mm, respectively), normal left ventricular ejection fraction (LVEF 56%) and mild concentric LV hypertrophy (posterior and septal wall thickness was 12-13mm). The right heart cavities and pericardium were within normal range.

Stroke and bleeding risk assessment revealed that our patient had a high stroke risk, as measured by a CHA_2DS_2-VASc score of 5. However, her risk of OAC-related bleeding was also increased, as measured by a HAS-BLED score of 4 (a history of prior bleeding, labile INRs, elderly and concomitant use of non-steroidal anti-inflammatory drugs). Follow-up gastrointestinal endoscopic examination showed that most of the gastric mucosal lesions have healed or near-healed. The patient was prescribed a non-vitamin K oral anticoagulant (NOAC) and advised to avoid the use of non-steroidal anti-inflammatory drugs or aspirin. At 6 months post discharge the patient was doing well, her haemoglobin was 126g/l, and CrCl was 50mL/min.

Discussion

Cardioembolic ischemic stroke is a deleterious complication of AF, associated with significantly greater mortality or permanent disability in comparison to stroke from other causes[1]. Thromboembolic events associated with AF can be effectively reduced using either NOACs or well-controlled VKAs[2]. However, in each patient with AF, the benefit of stroke reduction must be balanced against the risk of bleeding related to the use of oral anticoagulant therapy[3,4].

Our patient has a CHA_2DS_2-VASc score of 5 and is at high risk of stroke or systemic embolism. However, her bleeding risk is also high (a HAS-BLED score of 4) and she suffered a recent major bleeding event during the treatment with a VKA. Indeed, major or clinically relevant gastrointestinal bleeding is a serious medical condition,

Address for correspondence: Tatjana S. Potpara, MD, PhD, FESC, Cardiology Clinic, Clinical Centre of Serbia; School of Medicine, Belgrade University, Belgrade, Serbia, Visegradska 26, 11000 Belgrade, Serbia, Tel&Fax: +381 11 361 63 19; Email: tatjana.potpara@mfub.bg.ac.rs; tanjapotpara@gmail.com

especially in elderly patients with multiple comorbidities. It has been estimated that the annual risk of gastrointestinal bleeding in such AF patients not taking any antithrombotic therapy ranges between 0.3% and 0.5%[5]. In comparison to placebo, warfarin has been associated with a 3-fold greater risk of gastrointestinal bleeding, whilst concomitant use of warfarin and aspirin doubled the risk compared to monotherapy with warfarin[5]. In a meta-analysis of 43 randomized controlled trials comparing NOACs to standard care in different indications for oral anticoagulant therapy in a total of 151578 patients, the overall risk of gastrointestinal bleeding in patients taking NOACs was increased (Odds Ratio [OR] 1.45; 95% Confidence Interval [CI], 1.07–1.97), but there was a substantial heterogeneity amongst the trials. With respect to the indication for oral anticoagulant therapy, the risk of gastrointestinal bleeding was the highest among patients treated for arterial thrombosis (i.e., acute coronary syndrome), in whom NOACs were given concomitantly with other antithrombotic drugs (OR 5.21; 95% CI, 2.58–10.53), intermediate in patients with venous thrombosis (OR 1.59; 95% CI, 1.03–2.44) or AF (OR 1.21; 95% CI, 0.91–1.61) and the lowest in patients with orthopedic surgery (OR 0.78; 95% CI, 0.31–1.96)[6].

In a meta-analysis of the landmark NOACs trials of stroke prevention in patients with non-valvular AF[2], the use of NOACs (taken altogether) has been associated with increased risk of gastrointestinal bleeding in comparison to adjusted-dose warfarin (Relative Risk [RR] 1.25; 95%CI, 1.01-1.55, p=0.043)[2]. However, the difference was driven by the increased risk of gastrointestinal bleeding with the use of dabigatran 150mg-dose, rivaroxaban or edoxaban 60mg-dose, whilst the use of dabigatran 110mg-dose or apixaban 5mg-dose was associated with comparable gastrointestinal bleeding event rates as was the use of adjusted-dose warfarin[2,7].

Importantly, antithrombotic drugs such as aspirin or thienopyridines (e.g., clopidogrel), or non-steroidal anti-inflammatory drugs may cause a direct gastrointestinal mucosal damage, whilst oral anticoagulants can only facilitate bleeding from the pre-existing gastrointestinal lesions[8,9]. Although previous gastrointestinal bleeding event is a risk factor for future bleeding events in AF patients taking oral anticoagulant therapy[10], prior gastrointestinal bleeding is not an absolute contraindication for long-term oral anticoagulant therapy, especially in AF patients at high risk of stroke or systemic embolism[11]. Indeed, it has been shown that permanent discontinuation of warfarin post gastrointestinal bleeding was associated with increased rates of stroke and death in AF patients[12]. However, the timing of oral anticoagulant therapy restart is of key importance to avoid unnecessary complications. Hence, the exact timing of oral anticoagulant therapy restarting should be guided by the cause and severity of gastrointestinal bleeding and the patient's stroke risk level. Once the haemostasis post excision of a gastrointestinal tumour has been achieved or healing of the gastrointestinal mucosa has been confirmed, oral anticoagulant therapy can be safely restarted. However, in patients with multiple gastrointestinal angiectasias, the increased risk of gastrointestinal bleeding will remain[13].

Importantly, the decision to use oral anticoagulant therapy for thromboprophylaxis in AF requires the assessment of bleeding risk associated with the use of oral anticoagulants. Elevated HAS-BLED score itself should not be the reason to deny oral anticoagulant therapy, but should flag-up the patients at higher bleeding risk for regular, more intense clinical follow-up upon identifying and addressing the modifiable bleeding risk factors. Although the latest European Society of Cardiology (ESC) Guidelines on the management of AF do not formally recommend the use of HAS-BLED or other bleeding risk scores for the assessment of bleeding risk in AF patients in whom the use of oral anticoagulant therapy is considered, the correction of modifiable bleeding risk is strongly recommended[11]. Hypertension is a component of the HAS-BLED score, but scores 1 point only if uncontrolled (that is, if the systolic blood pressure persists above 160mmHg despite treatment). Thus, our patient has a well-controlled blood pressure. Her age and a history of prior bleeding event cannot be modified, but the use of non-steroidal anti-inflammatory drug can (and has been corrected). Since her INRs were labile, she could be advised to continue a VKA with a strict INR monitoring and strict diet modification, or she could be prescribed a NOAC.

Which of the two choices would be adequate for our patient? Her SAMe-TT_2R_2 score (see Table 1)[14] is >2 (that is, female sex, tobacco us [renal insufficiency is of moderate severity, hence not encountered in the score calculation]), thus predicting that she is not likely to do well on warfarin[15]. Indeed, her INRs were labile, and she ultimately suffered a major gastrointestinal bleeding during concomitant use of non-steroidal anti-inflammatory medication. According to her SAMe-TT_2R_2 score value of >2, the patient should have been prescribed a NOAC from the beginning.

When choosing a specific NOAC for our patient, her individual risk profile should be the principal driver of the ultimate medication choice. In particular, our patient is >75 years old, has a moderate renal failure, diabetes mellitus and a history of recent gastrointestinal

Table 1. The SAMe-TT_2R_2 score[14].

	Clinical parameter	Points
S	Sex (female)	1
A	Age (<60 years)	1
Me	Medical history*	1
T	Treatment (interacting drugs, e.g., amiodarone)	1
T	Tobacco use (within 2 years)	2
R	Race (non-Caucasian)	2
Max. points		8

*More than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease.

bleeding. In the landmark NOACs trials in AF, the use of dabigatran 110mg twice daily, apixaban 5mg twice daily or edoxaban lower-dose regimen (30mg or 15mg once daily) was associated with comparable risk of major or clinically relevant gastrointestinal bleeding relative to warfarin[7]. Edoxaban is not approved in Serbia, which narrows the choice to either dabigatran 110mg twice daily or apixaban 5mg twice daily.

Importantly, a sub-analysis of the RE-LY study of dabigatran for stroke prevention in non-valvular AF compared with adjusted-dose warfarin revealed a significant interaction between the treatment and age. In brief, whilst in patients younger than 75 years dabigatran 110mg twice daily was safer than warfarin in terms of major bleeding, in those ≥75 years old the risk of major *extracranial* (mostly gastrointestinal) bleeding was similar with dabigatran 110mg twice daily and with warfarin[16]. In addition, dabigatran is mostly eliminated via the kidneys (approximately 80% of the ingested dose) and elderly patients with long-standing hypertension and diabetes mellitus may be prone to rapid, unpredictable decline in renal function exposing the patient to increased risk of bleeding related to the use of dabigatran. In contrast, apixaban has been shown to be even more beneficial (that is, safer) in patients with mildly or moderately reduced renal function than in those with normal kidney function with respect to the reduction of major bleeding risk[17]. In our patient, the benefit with apixaban may be slightly attenuated by the interaction of apixaban safety with the presence of diabetes mellitus (the reduction in major bleeding risk with apixaban relative to warfarin was less pronounced in diabetic compared to non-diabetic patients in a sub-analysis of the ARISTOTLE trial)[18], but apixaban was still at least as safe as warfarin in terms of the risk of major bleeding events.

Finally, a non-pharmacological option for AF-related stroke prevention using percutaneous transcatheter left atrial appendage occlusion might be considered. However, more data are needed to better define the role of such treatment for stroke prevention in AF and, presently, such treatments most likely should not be used outside the randomized clinical trial setting. Indeed, the latest ESC AF guidelines recommend that the left atrial appendage occlusion may be considered for stroke prevention in AF patients with contraindications for long-term anticoagulant treatment such as, for example, a previous life-threatening bleed without reversible cause (Class of recommendation IIb, Level of evidence B). However, our patient had neither a life-threatening bleeding nor an irreversible cause of bleeding. Indeed, at 6 months post discharge, our patient was doing well on a NOAC.

References

1. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. Lancet 2016;388:806-17.
2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
3. Lip GY, Fauchier L, Freedman SB, et al. Atrial fibrillation. Nat Rev Dis Primers 2016;2:16016.
4. Lip GYH, Andreotti F, Fauchier L, et al. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. Thrombosis and haemostasis 2011;106:997-1011.
5. Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. International journal of clinical practice 2012;66:53-63.
6. Holster IL, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. Gastroenterology 2013;145:105-12 e15.
7. Potpara TS, Lip GY. Oral Anticoagulant Therapy in Atrial Fibrillation Patients at High Stroke and Bleeding Risk. Prog Cardiovasc Dis 2015;58:177-94.
8. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. Bmj 2006;333:726.
9. Lanas A, Wu P, Medin J, Mills EJ. Low doses of acetylsalicylic acid increase risk of gastrointestinal bleeding in a meta-analysis. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2011;9:762-8 e6.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138:1093-100.
11. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European heart journal 2016;37:2893-962.
12. Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. Archives of internal medicine 2012;172:1484-91.
13. Desai J, Granger CB, Weitz JI, Aisenberg J. Novel oral anticoagulants in gastroenterology practice. Gastrointestinal endoscopy 2013;78:227-39.
14. Lip GY, Haguenoer K, Saint-Etienne C, Fauchier L. Relationship of the SAMe-TT(2)R(2) score to poor-quality anticoagulation, stroke, clinically relevant bleeding, and mortality in patients with atrial fibrillation. Chest 2014;146:719-26.
15. Roldan V, Cancio S, Galvez J, et al. The SAMe-TT2R2 Score Predicts Poor Anticoagulation Control in AF Patients: A Prospective 'Real-world' Inception Cohort Study. The American journal of medicine 2015;128:1237-43.
16. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363-72.
17. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. European heart journal 2012;33:2821-30.
18. Ezekowitz JA, Lewis BS, Lopes RD, et al. Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial. Eur Heart J Cardiovasc Pharmacother 2015;1:86-9.