Case Report

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

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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 Ratio (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.

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 CHA²DS²-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. Thromboembolic events associated with AF can be effectively reduced using either NOACs or well-controlled VKAs. 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.

Our patient has a CHA²DS²-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,
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%. 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. 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).

In a meta-analysis of the landmark NOACs trials of stroke prevention in patients with non-valvular AF, 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). 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.

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. Although previous gastrointestinal bleeding event is a risk factor for future bleeding events in AF patients taking oral anticoagulant therapy, 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. 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. 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.

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. 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-TT2R2 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

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*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. 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. 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. 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), 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