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Case report

GENERATION X – CHALLENGES IN ANTICOAGULATION!

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Abstract

Atrial fibrillation (AF) increases an individual's risk of stroke by 4 to 6 times on average. The risk increases with age. In people over 80 years old, AF is the direct cause of 1 in 4 strokes. In these cases, anticoagulation therapy is recommended for primary prevention and secondary stroke prevention. Direct oral anticoagulants (DOACs) such as Rivaroxaban are preferred over Vitamin K antagonists (VKA), according to the latest guidelines. To present interesting and challenging cases from the clinical practice and discuss use of Rivaroxaban in primary and secondary prevention in patients with AF and stroke.

In November 2022 we organized a two-day workshop, under the auspices of the pharma company Bayer d.o.o. Ljubljana-Representative Office Skopje, Macedonia. Neurology and Cardiology residents presented 10 clinical cases, under the mentorship of respective specialists, experts in their fields. Clinical features, laboratory analysis, neuroimaging findings and contemporary management of each case were discussed in detail. Designated mentors presented the latest guidelines and recommendations regarding use of Rivaroxaban in primary and secondary prevention in patients with AF and stroke.

Below we present 10 clinical cases and describe in detail their physical and neurological condition, laboratory and imaging findings and therapeutic approach.

Keywords: primary prevention, secondary prevention, anticoagulation therapy, direct oral anticoagulants, rivaroxaban, atrial fibrillation, ischemic stroke, haemorrhagic stroke

Introduction

Atrial fibrillation (AF) increases an individual's risk of stroke by 4 to 6 times on average[1]. The risk increases with age. In people over 80 years old, AF is the direct cause of 1 in 4 strokes[2]. In these cases, anticoagulation therapy is recommended for primary prevention and secondary stroke prevention. Direct oral anticoagulants (DOACs) such as Rivaroxaban are preferred over Vitamin K antagonists (VKA), according to the latest guideline[3-5].

To present interesting and challenging cases from the clinical practice and discuss use of Rivaroxaban in primary and secondary prevention in patients with AF and stroke.

Material and methods

In November 2022 we organized a two-day workshop, under the auspices of the pharma company Bayer d.o.o. Ljubljana-Representative Office Skopje, Macedonia. Neurology and Cardiology residents presented 10 clinical cases, under the mentorship of respective specialists, experts in their fields. Clinical features, laboratory analysis, neuroimaging findings and contemporary management of each case were discussed in detail. Designated mentors presented the latest guidelines and recommendations regarding use of Rivaroxaban in primary and secondary prevention in patients with AF and stroke.

Results

Below we present 10 clinical cases and describe in detail their physical and neurological condition, laboratory and imaging findings and therapeutic approach.

Case series:

Patient 1: Use of Rivaroxaban as a monotherapy in a patient with AF, stroke and polycythemia vera

A 69-year-old male patient presenting with right-sided weakness and motor dysphasia was admitted to the University Clinic for Neurology. Comorbidities included paroxysmal AF, hypertension, dyslipidemia. The patient was with tachycardia and tachypnea, with presence of bilateral basal crepitations on auscultation, and a drop in oxygen saturation to 84% on/in ambient air. Neurological examination revealed motor dysphasia, right-sided motor weakness with pyramidal features, with increased muscle-tendon reflexes and positive Babinski sign. National Institute Health Stroke Scale (NIHSS) score was 12, Glasgow Coma Scale (GCS) was 13 and modified Rankin Scale (mRS) was 3. Braincomputer tomography (CT) scan showed an ischemic stroke in the left middle cerebral artery (Figure 1).

CT of the lungs showed bilateral findings of consolidation and pleural effusion in the basal parts (Figure 2). Electrocardiogram (ECG) showed signs of AF. Color duplex sonography (CDS) of the neck blood vessels was normal. Laboratory evaluations showed increased hemoglobin and hematocrit levels, increased degradation products and inflammatory markers. Other molecular diagnostic tests indicated by the hematologist established the diagnosis of polycythemia vera. After treatment of 2 weeks, the patient was discharged in an improved condition, with significantly improved laboratory findings. He was prescribed a full dose of Rivaroxaban of 20 mg q.d., together with gastroprotective and antihypertensive therapy. His CHA2DS2-VASc score (i.e., congestive heart failure, history of hypertension, age ≥75 years, diabetes, prior stroke, vascular disease, age 65 to 74, sex category) was 5 (high) and HAS BLED (i.e., hypertension, abnormal liver or renal function, stroke, bleeding, labile international normalized ratio, elderly age >65, drugs or alcohol) score was 3 (high).

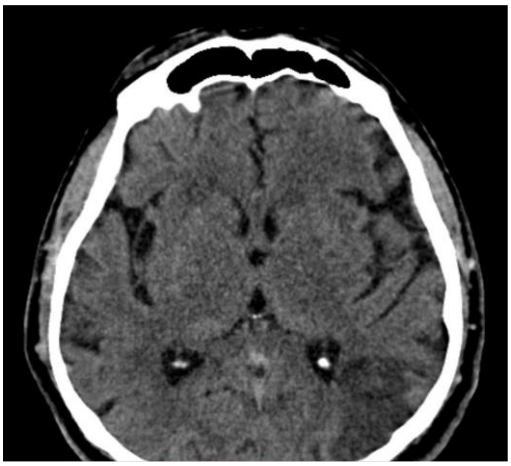

Fig. 1. CT of the brain: ischemic stroke in the left posterior parietal region, vascular terittory of left MCA

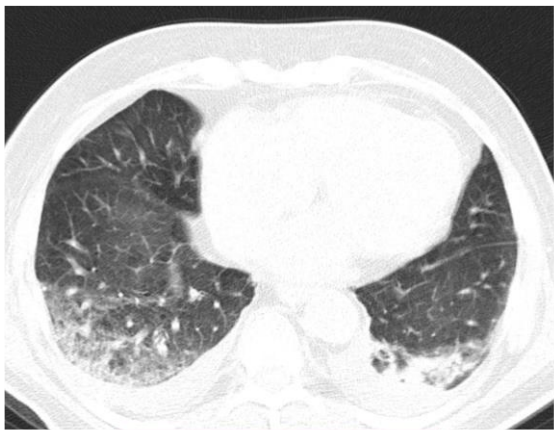

Fig. 2. CT of the lungs: bilateral findings of consolidation and pleural effusion in the basal parts

This led us to the decision to involve rivaroxaban in the prescribed therapy on discharge. Treatment dilemma was the combination of acetylsalicylic acid (ASA) prescribed from the hematologist and DOAC which was indicated because of the AF and his high CHA2DS2-VASs score. This problem represents a therapeutic challenge, due to the risk of thrombosis on one hand, and bleeding on the other. Since official protocols for the given situation are lacking, isolated cases indicate that the choice of DOAC as monotherapy is a safe and suitable one.

Patient 2: Anticoagulation in a patient with paroxysmal AF and CHA2DS2-VASc score 1

A 54-year-old male patientwas examined at the University Clinic for Cardiology due to fatigue and excessive sweating during physical activity. Past medical history revealed arterial hypertension, cardiomyopathy (moderate dilatation of the left ventricle, moderate mitral regurgitation and ejection fraction of 40%) and persistent AF detected 2 months earlier (treated unsuccessfully with cardioversion twice with DCES 200J). He was taking Amiodarone 200mg b.i.d., Metoprolol succinate 95 mgb.i.d, Rivaroxaban 20 mg q.d., Lercanidipin 10 mg q.d., Rampiril/ Hydrochlorothiazide 5/15 mg q.d. and Atorvastatin 10 mg q.d. On initial evaluation,the patient had blood pressure of 130/80 mmHg, heart rate was 120 beats per minute with AF

demonstrated on ECG (Figure 3), and his body mass index was 29.2. During hospitalization the patient underwent coronarography with normal results and there was another attempt for electrical cardioversion with DCES 200J and 360J, but was once again unsuccessful. On discharge, his ECG still showed AF with a heart rate of 85 beats per minute. The patient was discharged on: Metoprolol succinate 95 mg b.i.d.; Digoxin 0.25 mg q.d.; Rivaroxaban 20 mg q.d.

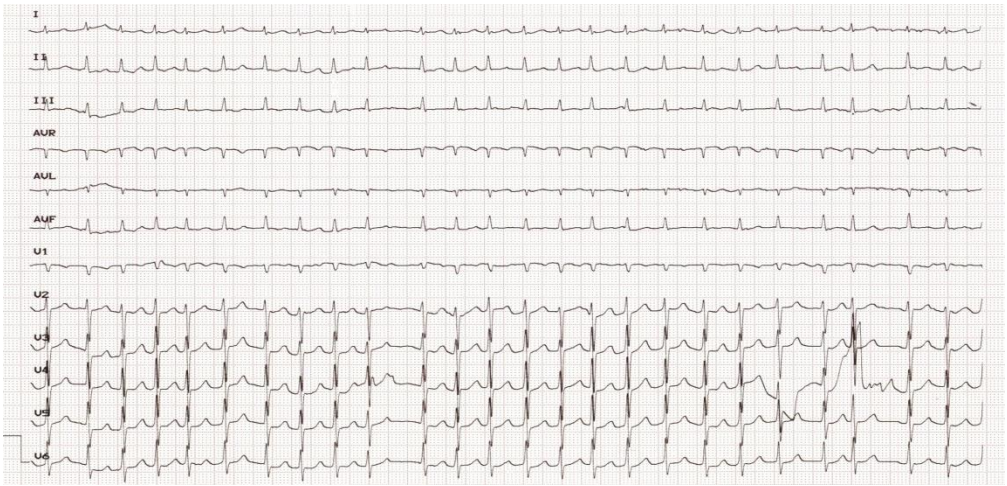

Fig. 3. ECG showing AF

One week after discharge it was noticed on ECG that the patient had spontaneous conversion to sinus rhythm and during the following visit he was recommended "Pill in the pocket" strategy for hearth rhythm control with Flecainide. His CHA2DS2-VASc score was also reduced to 1. Since he had more frequent episodes of paroxysmal AF, a decision for radiofrequency PVI ablation was done. New therapy was: Flecainide 50mg b.i.d., Rivaroxaban 20mg q.d., Metoprolol 95mg q.d. New episodes of arrhythmia were not noticed. There have been changes in the European Society of Cardiology recommendations regarding stroke risk management in pericatheter ablation[4]. The updated 2020 ESC guideline with class of recommendation I suggests that after AF catheter ablation, it is recommended: systematic anticoagulation with warfarin or a DOAC to be continued for at least 2 months post-ablation, and long-term continuation of systemic anticoagulation beyond 2 months post-ablation is based on a patient's stroke risk profile and not on the apparent success or failure of the ablation procedure. Finally, are all CHA2DS2-VASc risk factors created equal? An assessment of stroke risk among 34,470 patients with CHA2DS2-VASc scores of 1 or 2 was done and the conclusion was that ischemic stroke risk varied significantly across specific risk factors in patients with CHA2DS2-VASc scores = 1 or 2[6]. Therefore, OAC decisions in these patients should consider individual risk factors rather than the aggregate score alone.

Patient 3: Cardioversion in a patient with persistent AF and diabetes mellitus type II

A 71-year-oldmalepatient was examined at the University Clinic for Cardiology with complaints of fatigue and irregular heartbeat that appeared 1 month before the visit. Past medical history revealed diabetes mellitus type II treated with Glucophage 500mg q.d. and Insulin Humulin N 16+0+16 IE. On initial evaluation his blood pressure was 130/80 mmHg and heart rate was 135 beats per minute. Transthoracic echocardiogram was performed 6 months ago, with normal heart

morphology and ejection fraction of 65%. His ECG demonstrated AF with irregular heart activity and without noticeable P-waves (Figure 4). His CHA2DS2-VASc score was 2 (1 for diabetes and 1 for age). His HAS-BLED score was 1 (age above 65 years) with estimated bleeds per 100 patient-years of 1.02. Anticoagulation was recommended because the patient's CHA2DS2-VASc score was 2 and HAS-BLED score was lower than 3, so initiation of anticoagulation was safe without the need of evaluation and modifying the modifiable risk factors. The patient was recommended to take Rivaroxaban 20mg q.d. Estimated GFR was 109mL/min.

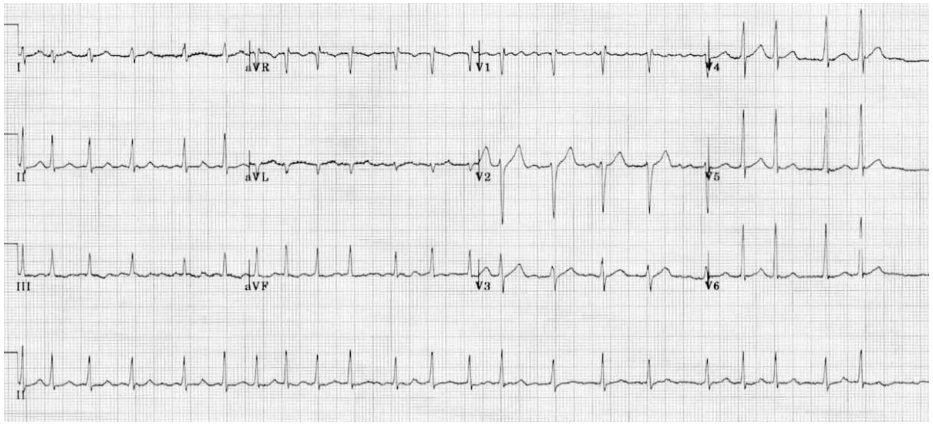

Fig. 4. ECG showing persistent AF with irregular heart activity and without noticeable P-waves

Treatment with selective beta-1 blocker was introduced (Metoprolol succinate 95mg q.d.) due to heart rate greater than 110 beats per minute. Four weeks after the initial visit, he was still complaining of fatigue and AF was again demonstrated on ECG. After treating with propofol intravenously, adhesive electrode pads were placed in anterior-posterior position and biphasic electrical shock was given with energy of 120J synchronized with R-wave. The patient was converted to sinus rhythm. This patient had diabetes, which is an independent risk factor for AF, even though they share common antecedents such as hypertension and obesity. Autonomic dysfunction in diabetes is the reason behind frequent asymptomatic episodes in these patients. Intensive glycemic control is not proven to change the outcome of AF, but treatment with Metformin lowers the risk for this condition.

For safe cardioversion in patients with unknown duration or duration of AF longer than 48 hours, transesophageal echo or anticoagulant treatment is recommended for at least 3 weeks. Antiarrhythmic treatment before electrical cardioversion increases the success for conversion in sinus rhythm. Maintenance of sinus rhythm 3 months after cardioversion is associated with a significant quality of life improvement.

Patient 4: Rivaroxaban for secondary stroke prevention in patients with AF

A 73-year-old male patient asked for medical assessment at the University Clinic for Cardiology due to dyspnea, dysphasia and right-sided hemiparesis. On initial evaluation his blood pressure was 180/100 mmHg, respiratory rate was 20/minute and oxygen saturation 89%. Laboratory analyses were as follows: Tp I 12,8 ng/L, CRP 33mg/L, WBC 13.3, INR 1,6, eGFR 73ml/min. Past medical history revealed hypertension, heart failure, permanent AF, diabetes mellitus type II and history of ischemic stroke. Additional scores were also calculated: CHA2DS2-VASc score was 7, HAS-BLED score was 5 and NIHSS score was 17. The patient was currently treated with Lisinopril, Spirinolactone, Bisoprolol, Atorvastatin and Acenocoumarol [medical records showed

that the patient had low time in therapeutic range (TTR), with international normalized ratio (INR) values of 1,3; 2,5; 0,9; 1,4 and 1,6]. Magnetic resonance imaging (MRI) of the brain showed bilateral vasculopathic lesions, global cortical atrophy and expanded ventricular system. Ischemic sequelae in the left occipital lobe and left insular cortex were registered. During hospitalization the patient was treated with diuretics, antibiotics, low-molecular weight heparin (LWMH), insulin, antihypertensive, lipid and glucose lowering agents. His condition improved and on discharge blood pressure was reduced to 135/80 mmHg, oxygen saturation was 94%, respiratory rate was 16 and heart rate 105/min. His neurological examination also improved and NIHSS was scored as 9 on discharge. He was recommended a new therapy with Furosemide 40mg q.d., Rivaroxaban 20 mg q.d., Insulin Novomix 30 36IE, Ramipril 10mg q.d., Spironolactone 25 mg q.d., Atorvastatin 40 mg q.d. and Metformin 1000mg q.d. Almost 39% of patients do not achieve satisfactory TTR. The compliance and percentage of TTR is reduced over time. Approximately 3/4 of patients with stroke have subtherapeutic INR (<2.0), and 10% of patients with INR between 2.0 and 3.0have stroke. Also, the bleeding incidence of long-term VKA therapy is 10-17%/year. Between 2 and 5% of patients have major bleeding and 0.2-0.4% have fatal intracranial hemorrhage[7]. Thus, DOACs are preferred therapeutic choice in AF patients, due to their safety, easy dosing, predictable pharmacodynamics and less interactions with drugs and food.

Patient 5: To DOAC or not to DOAC?/To prescribe/give DOAC or not? What is to be done?

A 67-year-old male patient was admitted to the University Clinic for Neurology due to severe frontal headache, instability and speech deterioration. Approximately three hours before the current admission, the patient had suddenly started behaving unusually and speaking incoherently. Comorbidities includedhypertension, diabetes mellitus, hyperlipidemia and AF for which he had a long-term treatment with Acenocoumarol, Lisinopril 20 mgq.d., Amlodipine 10mgq.d., Bisoprolol 2.5 mgq.d., Atorvastatin 20mgq.d., Insulin Humulin 32+22 IE. Neurological exam revealed altered level of consciousness (drowsiness), right-sided motor deficit of mild degree, right-sided central facial palsy, and positive Babinski sign on the right. The calculated scores on admission were: NIHSS=9, mRS=4, GCS=14. ECG showed absent P waves and irregular QRS complexes with varying P-R intervals, i.e. AF and high levels of blood pressure (270/120 mmHg).Routine blood test results showed increased levels of WBC=16.02 10^9/L; CRP= 59.9 mg/dl; glucose=10.7 mmol/L; CK=1234 U/L, LDH=215 U/L and D-dimer= 728 ng/ml. Brain CT scan showed left hyperdense media sign accompanied with cytotoxic edema of the left temporal lobe (Figure 5). Treatment with antiedematous therapy was initiated, accompanied with antithrombotic, antihypertensive, antilipemic, insulin therapy, LMW Hand other symptomatic therapy. Control CT scan performed after 24 hours confirmed a cortical-subcortical infarction in the left temporal and parietal lobes, respectively in the vascular territory of the left MCA, with dimensions 60x27 mm and a slightly compressed left lateral ventricle (Figure 6). Carotid color duplex sonography showed hyperechogenic plaque at the level of the bifurcation of the left common carotid artery (CCA) and at the starting portion of the left internal carotid artery (ICA).

Medical electronic system records showed that since his diagnosis of AF in 2019, the patient visited the transfusion medicine service only 5 times, with values of INR levels (1.1, 2.2, 1.2, 1, 1) under therapeutic range. After a 12-day-hospital stay, the patient was discharged from the clinic in relatively stable neurological condition with Rivaroxaban 20 mg q.d. and other symptomatic therapy. The choice of anticoagulation was easily made due to the benefit of the DOACs, i.e.

improvement of patient's quality of life and prevention of ischemic strokes. Therefore, in respect of our case, we say: Better DOAC today, than stroke tomorrow!

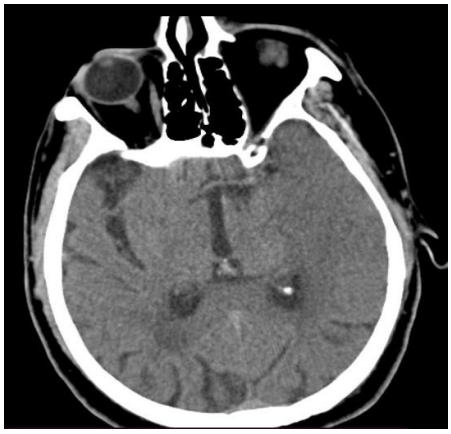

Fig. 5. Axial native CT scan showing cytotoxic edema in the left temporal lobe (territory of left MCA)

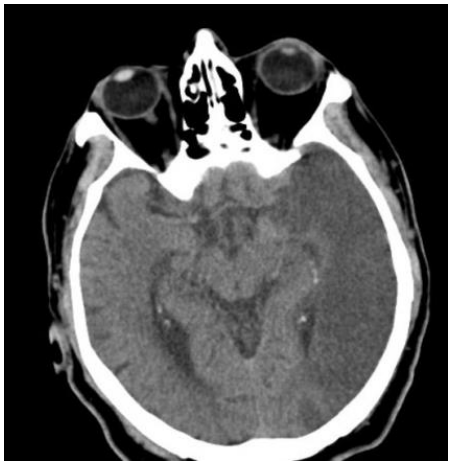

Fig. 6. Axial native CT scan showing hypodense lesion in the cortical-subcortical parts of the left temporal and parietal lobes (left MCA territory) with dimensions 60x27 mm and slightly compressed left lateral ventricle

Patient 6: Safety profile in patients on combined antithrombotic therapy

This is the case of a 58-year-old male patient who came to the University Clinic for Cardiology due to palpitations and chest pain. Past medical history revealed hypertension and myocardial infarction (MI). Previous medications included ASA 100mg q.d., Prasugrel 10mg q.d., Rosuvastatin 40mg q.d., Carvedilol 6.25 mg q.d., Perindopril 2 mg q.d., Spironolactone 25 mg q.d., Furosemide 20 mg q.d. ECG on admission showed AF. After chemical cardioversion with amiodarone, ECG registered sinus rhythm. Laboratory analysis showed increased levels of troponin (3585.2 ng/L); other parameters were normal. Echocardiography registered increased dimensions of the left ventricle and slightly reduced global systolic function, with akinesis of the basal and mid-segment of the posterior lower wall with increased aortal dimensions at the level of the sinotubular

junction. This patient fulfilled the criteria for extended treatment with a second antithrombotic agent, because of his high thrombotic risk (history of recurrent MI, history of stent thrombosis on antiplatelet treatment). Treatment options for extended dual antithrombotic or antiplatelet therapies include use of ASA 75-100 mg q.d. with Rivaroxaban 2.5 mg b.i.d., or with Clopidogrel 75 mg/d, Prasugrel 10 mg/d (5 mg/d if body weight is < 60 kg or age >75 years) and Ticagrelor 60/90 mg b.i.d., respectively. European Cardiology Society Guidelines (2017) recommend dual therapy (oral anticoagulation in combination with clopidogrel) in patients with a high risk of bleeding[8]. ACS guidelines recommended DAPT for up to 1 year after the acute event in patients without indication for OAC and high-risk patients might require an even longer DAPT duration. In high bleeding-risk ACS patients, however, current ESC guidelines allow for shorter DAPT durations (3-6 months). If AF develops during the first year after an ACS, there is an indication for anticoagulation; a DOAC should be started and the need for continuing DAPTshould be carefully weighed against the increased bleeding risk. Following 1 month after the event, Aspirin can be stopped in the majority of such patients.

Patient 7: Rivaroxabandosing in patients with AF and chronic kidney disease

This is the case of a 67-year-old male patient hospitalized at the University Clinic for Cardiology due to decompensated heart failure (DFH). Past medical history revealed AF, percutaneous coronary intervention (PCI)/stenting, diabetes and chronic kidney disease (CKD) (stage II). Previous medications included Rivaroxaban 20mg q.d., Spironolactone 25 mg q.d., Furosemide 20mg q.d., Ramipril 2.5 mg q.d., Metoprolol 95mg q.d., Atorvastatin 20 mg q.d., Metformin 1000mg b.i.d..Physical examination showed edema on the lower extremities, and the other parameters were normal.

ECG on admission showed AF, cardiac echocardiogram confirmed the diagnosis of DHF; laboratory blood analysis showed increased levels of glucose (14.78 mmol/L), and the other parameters were normal. The patient was treated with intravenous infusion of 100 ml sodium chloride 0.9%, withamp. Furosemide 40 mgb.i.d, Rivaroxaban 20mg q.d., Metoprolol 95mg q.d., Ramipril 2.5mg q.d., Spironolactone 25mg q.d., Atorvastatin 20mg q.d. His estimated glomerular filtration rate (eGFR) was 41.8 ml/min, CHA2DS2-VASc score was 4 and HAS-BLED score was 3. According to the European Medicines Agency, the recommended dose of Rivaroxaban is 20 mg once daily, which is also the recommended maximum dose. For patients with moderate renal impairment (creatinine clearance 30- 49 ml/min) the recommended dose is 15 mg once daily. So, due to his impaired renal function, after the stabilization of his medical condition, on the 8th day of the hospitalization, our patient was discharged home with prescribed anticoagulant therapy Rivaroxaban 15 mg q.d., with regular oral antidiabetic and cardiologic therapy. After one month, on the control examination the patient showed signs of cardiac compensation and improved eGFR (68.6 ml/min). We therefore discussed if this patient should be switched to Rivaroxaban 20 mg q.d. instead of 15 mg q.d. Also, we discussed how often should the degradation products and renal function be checked. Serum creatinine should be measured and renal function should be assessed at baseline in all patients starting a DOAC and at least once a year thereafter. Local guidance states that renal testing frequency should be every 6 months if CrCl 30-60 ml/min (apixaban, dabigatran, edoxaban, rivaroxaban) and every 3 months if CrCl 15-30 ml/min (apixaban, edoxaban, rivaroxaban). DOACs have been shown to be more effective and safer compared to VKAs in patients with AF and CKD (GFR>15 ml/min).

Patient 8: Rivaroxaban in a patient with AF, dilated cardiomyopathy, hyperthyroidism and ischemic stroke, treated with intravenous thrombolysis

A 49-year-old male patient was examined at the University Clinic for Neurology due to sudden left-sided weakness and altered speech manifested 2 hours before admission. Comorbidities included hyperthyroidism diagnosed 12 years ago treated with Thyrozol 20mg q.d. but with poor medication adherence. Ten years later, he was diagnosed with dilated cardiomyopathy and AF and treatment was recommended with acenocumarol that was eventually interrupted 2 year later. Currently he was treated with Bisoprolol 2,5 mg q.d., ASA 100mg q.d., Furosemide 20 mg q.d. and Spironolactone 25 mg q.d. Blood pressure was 140/80 mmHg, ECG showed AF with heart rate of 120 beats per minute. Neurological examination revealed head and gaze deviation to the right, dysarthria, dysphagia, left-sided central facial palsy, acute motor deficit on the right side with positive Babinski sign. NIHSS score was 11, mRS was 5 and GCS was 15. Initial CT scan was normal. The patient was eligible for intravenous tissue-type plasminogen activator (IV tPA), which was given in a total dose was 60.75mg. Afterwards NIHSS score was 9. Control CT scan showed ischemic stroke in evolution in the territory of right MCA. Cardiology consultation confirmedAF. Color duplex sonography of the neck blood vessels was normal. On discharge neurological examination was improved with NIHSS of 3 and mRS of 1. CHA2DS2-Vas score was 1, which put him in the category with moderate risk for thrombotic events and anticoagulation was recommended. For secondary stroke prevention, anticoagulant therapy was recommended with Rivaroxaban 20 mg q.d. and antiarrhythmic, antihypertensive and antithyroid agents. Patients with cardiomyopathy have a high thromboembolic risk, including symptomatic or asymptomatic peripheral artery thrombosis, pulmonary embolism and ischemic stroke. Hyperthyroidism is common endocrinological disorder that carries a higher risk for AF and higher risk for cardioembolic stroke. Recommendations for optimal treatment are required such as the decision for therapeutic *vs.* prophylactic anticoagulation and the type of anticoagulants.

Patient 9: Rivaroxaban in a patient with AF and ischemic stroke after treatment with intravenous thrombolysis

A 78-year-old female patient was brought to the University Clinic for Neurology due to a sudden right-sided weakness, inability to produce speech and decreased level of consciousness. Her past medical history revealed AF, hypertension, dyslipidemia, hemicolectomy (due to colorectal carcinoma) ten years before this event and history of a great saphenous vein thrombus. Current treatment included ASA 100mg q.d. (she stopped taking acenocoumarol 4 years ago due to lower gastrointestinal bleeding); Metoprolol 100mg q.d.; Losartan 100mg q.d.; Rosuvastatin 10 mg q.d.; Amlodipin 10 mg q.d. The initial patient assessment revealed a blood pressure of 165/90 mmHg, heart rate of 85 beats per minute, glucose level of 8.7 mmol/L and ECG showed AF with no visible P waves and irregular QRS complex. Head CT showed no hemorrhage and no ischemic changes. The patient fulfilled all inclusion criteria without any exclusion criteria for intravenous thrombolysis, and therefore the decision for treatment with IV tPA was done, with a NIHSS score of 23. Treatment went with no complications, with a NIHSS score of 22 after treatment. Carotid duplex sonography showed stenosis of the right ICA (60-70%) with initial hemodynamic disturbance and occlusion of the left ICA. Control CT scan revealed ischemic stroke in the left MCA, with a “hyperdense sign” of the left MCA. CT angiography confirmed the color duplex findings (Figure 7 and Figure 8, respectively). During hospitalization the patient was treated with antiedematous treatment, LMWH, antihypertensive, antipsychotic and gastroprotective agents. Her neurological exam improved, with NIHSS of 19, GCS of 10 and mRS of 5 at discharge. For

secondary stroke prevention, anticoagulant therapy was recommended – Rivaroxaban 20 mg q.d. and antiarrhythmic, antihypertensive, antilipemic and neuroprotective agents. Rivaroxaban was chosen as the optimal treatment of this patient with AF, carotid stenosis/occlusion and history of gastrointestinal bleeding.

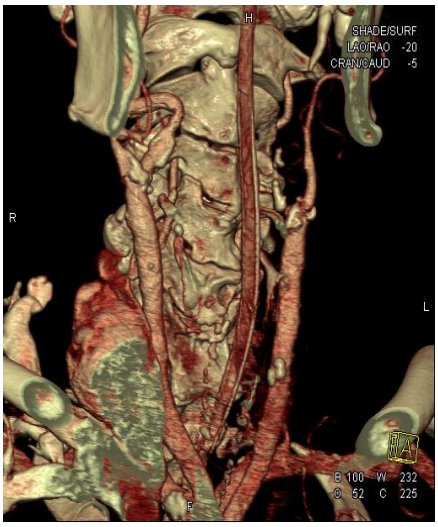

Fig. 7. CT angiography: occlusion of left ICA

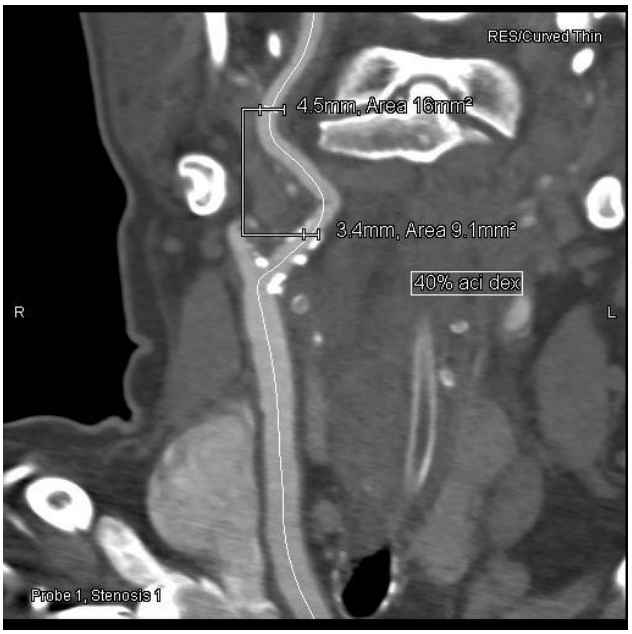

Fig. 8. CT angiography: stenosis of right ICA

Patient 10: Treatment of a patient with non-cardioembolic stroke

A 58-year-old malepatient was hospitalized at the University Clinic for Neurology due to acute onset of symptoms 5 days ago (slurred speech, dizziness, ataxia). Comorbidities included hypertension treated with antihypertensive therapy. Brain CT scan revealed a pontine infarction. On

admission, blood pressure was 160/90 mm Hg, pulse was rhythmic with HR 85/min. Neurological examination showed convergent strabismus, dysarthria, bradylalia, right dysmetria, ataxia and positive Babinski sign bilaterally. NIHSS score was 3, GCS 15 and mRS was 2. Laboratory blood and urine analysis was normal. Color duplex sonography of neck blood vessels showed at heromatosis of the carotid arteries with a stenosis up to 30% and 50% on the left and right side, respectively. Both vertebral arteries were tortuous, without hemodynamic repercussions. The patient was treated with antiedematous, antihypertensive, antilipemic and other symptomatic therapy. He was discharged in an improved neurological condition with a recommended dual antiplatelet therapy (DAPT) (ASA and Clopidogrel), statin and antihypertensive therapy. After the clinical evaluation, ECG, neuroimaging, laboratory studies, and color duplex sonography of the neck blood vessels, it was concluded that the patient has a pontine infarction of non-cardioembolic nature. Current guidelines for secondary prevention of non-cardioembolic stroke recommend use of DAPT for a duration of 21 days, followed by single antiplatelet therapy if the patient has suffered a mild stroke[5].

Discussion

We presented 10 challenging cases and discussed use of anticoagulation therapy with rivaroxaban in primary and secondary prevention in patients with AF. We also addressed specific risk factors and comorbidities of our patients (diabetes, chronic kidney disease, polycythemia vera, carotid stenosis/occlusion, previous MI, dilated cardiomyopathy, hyperthyroidism, stent restenosis and others) that affected the decision of the choice of the anticoagulation treatment.

AF is defined as irregular, uncoordinated electrical impulses of the atria which leads to ineffective atrial contraction. In atrial fibrillation, ECG will have no visible P waves and an irregular RR intervals. An episode lasting at least 30 seconds is diagnostic. There are three primary types of atrial fibrillation: paroxysmal, persistent and permanent AF. It is the most common type of arrhythmia in the population (with prevalence of 0.51% in 2016) and causes significant morbidity and mortality with prevalence increasing with age. In 2016, 7.6 million people above the age of 65 had AF with expected increase up to 89% by 2060[9]. Risk of ischemic stroke is 5 times higher in these patients and it causes 20-30% of all ischemic strokes. The ABC pathway for the holistic, integrated management of patients diagnosed with AF: "A" avoid stroke with anticoagulation; identify patients with low CHA2DS2-VASc score (0 for males and 1 for females). For patients with CHA2DS2-VASc score of 1 for males and 2 for females, anticoagulation with DOAC should be recommended. “B" for better symptom management with patient-centered, symptom directed decisions on rate or rhythm control; and "C" cardiovascular and comorbidity risk reduction, including lifestyle factors and psychological morbidity. As chronic oral anticoagulation for stroke prophylaxis reduces stroke risk and increases bleeding risk, several risk/benefit decision aids have been developed and validated. The most commonly used method is the CHA2DS2-VASc score. CHA2DS2 stands for Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes, previous Stroke/Transient Ischemic Attack (TIA). VASc stands for Vascular disease (peripheral arterial disease, previous MI, aortic atheroma), Age ≥ 65 years, Sex category (female). Each risk factor receives 1 point, with the exceptions of age greater than 75 years and Stroke/TIA, which receive 2 points each. In general, the higher the CHA2DS2-VASc score, the higher the annual stroke risk. For 0 score the annual risk of stroke is 0%, for 1 point it is 1.3%, for 2 points 2.2%, for 3 points 3.2%, for 4 points 4.0%, for 5 points 6.7%, for 6 points 9.8%, for 7 points 9.6%, for 8 points 6.7% and for 9 points the annual risk of stroke is 15%.

The already well-known ROCKET AF study showed that rivaroxaban was noninferior compared to warfarin in preventing stroke in patients with nonvalvular AF[10]. The current statement regarding the initiation of oral anticoagulant therapy following acute ischemic stroke, introduced in 2013 by the European Heart Rhythm Association of the European Society of Cardiology, is that it depends on the severity of the stroke, and consequentlythe delay of the anticoagulant initiation increases with the increasing stroke severity, due to the evidence that large infarcts are more likely to develop hemorrhagic transformation[11]. Therefore, in patients experiencing a transient ischemic attack (TIA), anticoagulant can be started after 1 day, in patients with mild stroke the preferred initiation of the OAC is after 3 days, in patients with moderate stroke after 6 days, and in patients with severe stroke after 12 days.

The 2021 AHA/ASA guideline for the prevention of stroke in patients with stroke and transient ischemic attack and AF recommend the following[5]:

1. In patients with nonvalvular AF and stroke or TIA, oral anticoagulation with DOAC is recommended in preference to VKA to reduce the risk of recurrent stroke – class and level of recommendation IA;
2. CHA2DS2-VASc scale is recommended to evaluate the risk of stroke. Patients with low risk of stroke should be identified and not treated with antithrombotic treatment (CHA2DS2-VASc = 0 for males and 1 for females) – class and levelof recommendation IA;
3. OAC is recommended for stroke prevention in patients with AF and CHA2DS2-VASc ≥ 2 for males and ≥ 3 for females – class and level of recommendation IA;
4. OAC could be recommended for stroke prevention in patients with AF and CHA2DS2 – VASc = 1 for males and 2 for females. Treatment should be individualized based on net clinical benefit – class of recommendation IIa and level of recommendation B;
5. Evaluation of bleeding risk should be done with formal assessment of risk factors, identification of non-modifiable risk factors and addressing modifiable risk factors. Patients with potentially high risk of bleeding should be identified and regularly controlled – class and level of recommendation IB.

Regarding the CHA2DS2-VASc score, recommendations are the following:

1. Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more. Class and Level of recommendation IA;
2. Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of 3 or more. Class and Level of recommendation IA;
3. Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA2DS2-VASc score of 1 considering individual characteristics and patient preferences. Class of recommendation IIa and Level of recommendation B;
4. Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA2DS2-VASc score of 2 considering individual characteristics and patient preferences. Class of recommendation IIa and Level of recommendation B;
5. Vitamin K antagonist therapy (INR 2.0-3.0 or higher) is recommended for stroke prevention in AF patients with moderate to severe mitral stenosis or mechanical heart valves. Class of recommendation I and Level of recommendation B;

6. Oral anticoagulation is initiated in patients with AF who areeligible for a DOAC (Apixaban, Dabigatran, Edoxaban and Rivaroxaban), a DOAC is recommended in preference to VKA. Class of recommendation I and Level of recommendation A;
7. When patients are treated with VKA, TTR should be kept as high as possible and should be closely monitored. Class of recommendation I and Level of recommendation A;
8. AF patients already on treatment with VKA may be considered for DOAC treatment if TTR is not well controlled despite good adherence, or if patient preference is without contraindications to DOAC (e.g. prosthetic valves). Class of recommendation IIb and Level of recommendation A.

Regarding the bleeding risk, recommendations are the following:

1. Blood pressure control in anticoagulated patients with hypertension should be considered to reduce the risk of bleeding. Class of recommendation IIa and level of recommendation B;
2. When Dabigatran is used, a reduced dose (110mg twice daily) may be considered in patients >75 years to reduce the risk of bleeding. Class of recommendation IIb and level of recommendation B;
3. In patients at high-risk of GI bleeding, a VKA or another DOAC preparation should be preferred over Dabigatran 150mg twice daily, Rivaroxaban 20mg once daily, or Edoxaban 60mg once daily. Class of recommendation IIa and level of recommendation B;
4. Advice and treatment to avoid alcohol excess should be considered in all AF patients considered for OAC. Class of recommendation IIa and level of recommendation C.

Recommendations for patients with a high bleeding risk:

1. Increased bleeding risk should not withhold us from (re-)starting anticoagulation therapy;
2. Instead, modifiable risk factors should be identified and managed.

Potentially modifiable bleeding risk factors are anemia, impaired kidney function, impaired hepatic function, and decreased platelet count. Modifiable bleeding risk factors are: hypertension (systole >160mmHg), labile INR or time in therapeutic range <60% in patients treated with VKA, avoiding of agents that provoke bleeding, such as antiaggregants or NSAID and excessive alcohol consumption (>8 drinks/week).

Is advanced age contraindication for anticoagulation?

The elderly have the highest risk for stroke. In the BAFTA study it was demonstrated that OAC were superior to acetylsalicylic acid for ischemic stroke prevention in patients >75 years (81.5±4.2years), with no significant difference for hemorrhagic complications[12]. That is why anticoagulant therapy in the elderly should not be limited, which is also demonstrated in other studies[10,13].

Conclusion

Our challenging cases re-affirm the safety profile of Rivaroxaban in selected patients and highlight the need of more studies on a larger scale that would determine the best options of anticoagulation in patients with AF and other comorbidities. DOACs are the preferred choice among OACs because of good safety profile, simple dosing, predictable pharmacodynamics and less drug interactions. DOAC are the new golden standard for primary and secondary prevention in patients with AF.

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