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Efficiency of the Decision-Making Module in the Personalized Choice of an Anticoagulant

Aim	To evaluate the effectiveness of the decision-making module in selecting an oral anticoagulant for patients with atrial fibrillation.
Material and methods	638 patients with atrial fibrillation aged 68.2±4.5 years were evaluated. The CHA2DS2-VASc, HAS-BLED, and 2MACE scales, the creatinine clearance calculator, and the Morisky-Green questionnaire were used.
Results	311 (48.75%) patients had paroxysmal atrial fibrillation, 138 (21.6%) had persistent atrial fibrillation, 44 (22.7%) had long-standing persistent atrial fibrillation, and 145 (22.7%) had permanent atrial fibrillation. Mean CHADS2-VASc scale score was 4.82; HAS-BLED scale score was 2.9; 2MACE score was 2.28; and compliance score was 3.52. 172 (26.9%) patients were treated with rivaroxaban; 166 (26%), with apixaban; 84 (13.2%), with dabigatran; 210 (32.9%), with warfarin; and 6 (1%), with acetylsalicylic acid.
Conclusion	The developed decision-making module is based on scientific justification of personalized selection of the oral anticoagulant and updates the knowledge on major issues of prescription.

Keywords	Personalized selection of anticoagulant; atrial fibrillation; algorithm
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Introduction

Several oral anticoagulants are currently available for treating patients with atrial fibrillation (AF). Although an appropriately selected anticoagulant can prevent adverse events and improve prognosis, anticoagulants can cause hemorrhagic complications; moreover, there is a high risk of developing thrombotic complications if the dose is not sufficient. When using vitamin K antagonists (VKAs) such as warfarin, it is necessary to monitor international normalized relations (INR) taking into account the peculiarities of food and drug interaction [1]. Since direct oral anticoagulants (DOACs) do not require blood clotting parameters to be monitored, randomized clinical trials (RCTs) and clinical practice generally prioritise DOACs [2].

Supported by a grant from the Russian Cardiology Society, cardiologists of the Kuzbass Scientific Society developed the «Personalized Selection of Anticoagulant in Atrial Fibrillation» decision-making module. This comprises a computer program based on an algorithm for selecting a DOAC in cases of AF while taking into account clinical guidelines, standards and instructions on the administration of anticoagulants (Certificate of state registration of the computer program "Personalized Selection of Anticoagulant in Atrial Fibrillation" No. 2019662306 dated 20/09/2019). The selection of an anticoagulant to form a register of AF patients takes into account information placed in the outpatient electronic record by a physician (Certificate of state registration of the computer program "Electronic Register of Patients with Atrial Fibrillation" No. 2019662305 dated 20/09/2019).

Aim

Evaluate the effectiveness of the "Personalized Selection of Anticoagulant in Atrial Fibrillation" module when matching the recommended anticoagulant and the anticoagulant ordered by the physician.

Material and methods

638 people from the AF patient register were included in the study carried out from July 2019 to March 2020. The study, which was approved by the Ethics Committee, followed the Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association Declaration of Helsinki. All patients signed the informed consent form to participate in the study.

The anticoagulant selection algorithm is based on the new Guidelines for Management of Atrial Fibrillation of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery according to the principle of first confirming arrhythmia and describing

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AF, then administering anticoagulant therapy, monitoring symptoms and managing concomitant pathologies [3].

The stroke and thromboembolism prevention algorithm includes several steps. Patients with mechanical prostheses and moderate to severe mitral stenosis receive warfarin. In other cases, patients at low risk of stroke are identified first; for such patients, anticoagulant and antithrombotic therapy is not prescribed. Stroke prevention is then evaluated using the CHA2DS2-VASc score, with the class of indications for DOACs and VKAs being determined by the score while keeping the time in therapeutic range (TTR) above 70%.

Correction of the modifiable risk factors of bleeding, which is considered in the decision-making module as defining the cardiologist's opinion, is carried out using the HAS-BLEAD score. The algorithm also takes into account the creatinine clearance calculation. In order to predict the risk of coronary complications, the 2MACE score is used. Treatment compliance is assessed using the Morisky-Green questionnaire.

Contingency tables were constructed using Pearson's chi-squared test for the qualitative analysis of the ratio of the anticoagulant drugs recommended by the computer program and actual prescriptions made at outpatient visits. The critical statistical significance level was 0.05. Statistical calculations were carried out using the standard software suite Statistica v.8.0.

Results

The study carried out in the outpatient clinic of the cardiology center from July 2019 to March 2020 comprised 638 patients (56.7% female) with an average age of 68.2 ± 4.5 years from the register of AF patients. 311 (48.75%) patients were registered as suffering from paroxysmal AF, 138 (21.6%) had persistent AF, and 145 (22.7%) patients had permanent AF. The mean CHA2DS2-VASc score was 4.82; NAS-BLED score – 2.9; 2MACE – 2.28; treatment compliance score – 3.52.

Signs of chronic heart failure were assessed according to the NYHA classification: functional class (FC) I in 56 (8.8%), FC II in 451 (70.7%), FC III in 120 (18.8%), and FC IV in 11 (1.72%) patients. Hypertension was reported in 588 (92.2%) patients, including stage 2 and stage 3 in 147 (23.04%) and 434 (68%) patients, respectively. History of ischemic stroke was registered in 64 (10%) patients; peripheral artery disease – 44 (6.9%); diabetes mellitus (SD) –103 (16.14%). In 23 (3.6%) cases, malignant neoplasms were diagnosed. The main cause of AF was coronary artery disease (48.1%); 22.47% of patients had a history of myocardial infarction. Coronary artery bypass grafting had been performed in 27 (8.8%) subjects and percutaneous coronary intervention, including stenting in 64 (20.8%) patients.

This study included an analysis of actual anticoagulant therapy and a therapy calculated using a personalized approach. Rivaroxaban was administered to 172 (26.9%) patients; apixaban – 166 (26%); dabigatran – 84 (13.2%); warfarin – 210 (32.9%); acetylsalicylic acid – 6 (1%) patients.

Based on our algorithm, rivaroxaban should have been recommended twice as often (p=0.0002). The use of apixaban and warfarin should have been reduced by 10% (p=0.0771) and 15% (p=0.0150), respectively (should be recommended to patients with prosthetic valves and moderate to severe mitral stenosis). Acetylsalicylic acid should not have been used in treatment of AF.

Discussion

According to the study, rivaroxaban should be a DOAC of choice for several reasons. In the first place, this is because the prevalence of AF increases with age [4]. Age is a key factor in developing an acute vascular catastrophe: the older the patient, the greater the risk. One in four 80-90-year-old patients are likely to have a stroke if they are not treated [5]. As confirmed by common risk assessment score in patients with AF, being aged over 65 years is a risk factor for ischemic and hemorrhagic complications, leading to a higher risk of complications from cardiac embolism [3].

The ROCKET AF study showed that, compared to warfarin, the use of rivaroxaban was accompanied by a lower risk of cardioembolic complications in elderly patients with AF (mean age 73 years), as well as reducing the risk of the most severe hemorrhagic complications, including fatal hemorrhage [6]. The benefits of rivaroxaban in the elderly populations from the ROCKET AF study were also confirmed in real-life clinical studies in patients of even older ages. For example, in the PREFER in AF program, which included patients with a mean age of 80 years, the use of rivaroxaban resulted in a 42% reduction in the total number of complications (ischemic and hemorrhagic) [7]. The results of the SAFIR AC study on a population of French geriatric patients (mean age 86 years) demonstrated the use of rivaroxaban to lead to a statistically significant reduction in the risk of severe hemorrhage, including intracranial, as compared to warfarin [8].

The known risk factors for bleeding during anticoagulant treatment are much the same as those contributing to thromboembolic complications in patients with AF. According to the Swedish cohort study of more than 150 thousand patients with AF, the primary endpoint in the DOAC therapy was the net benefit defined as the number of prevented ischemic strokes with anticoagulants minus the number of excess intracranial bleeding events [9].

The risk of developing thromboembolic complications in patients with AF, even those with high HAS-BLED scores,

is always higher than the risk of bleeding. At the same time, the increased risk of hemorrhagic complications should not be the basis for not using DOACs, since the cumulative clinical benefit of these therapies is higher in patients with an increased risk of hemorrhagic complications [3].

If the risk of bleeding is high, the modifiable risk factors should be corrected, and patients examined more frequently to prevent the development of hemorrhagic complications. The modifiable factors include arterial hypertension or increased systolic blood pressure, concomitant administration of antiplatelet and nonsteroidal anti-inflammatory drugs, alcohol misuse, transient heparin therapy, dangerous hobbies/activities and labile INR [3].

According to the latest recommendations (as of 2020), the management of patients with AF does not just involve stroke prevention, but also implies comprehensive patient protection, including the management of cardiovascular risk factors, lifestyle interventions and improvement of compliance, as well as the administration of anticoagulants. Much attention is paid to concomitant diseases, such as DM, which comprises one of the most frequent concomitant diseases in AF. Data from population studies confirm DM to constitute an independent risk factor of AF [10]. Patients with DM and AF have a significantly higher risk of cardiovascular complications and all-cause mortality than those without DM. Patients with DM and AF have a more adverse prognosis: higher risk of all-cause death by 61%, cardiovascular death by 77%, as well as a higher rate of chronic heart failure and stroke by 68% [11].

A combination of high risk of stroke and chronic kidney disease also contributes to the increased risk of cardiovascular death. The use of rivaroxaban in patients with creatinine clearance of 30–49 mL/min was characterized by much greater safety as compared to warfarin along with comparable efficacy. A 61% reduction in the risk of fatal bleeding during the administration of rivaroxaban [12] was of particular significance.

The high potential of using rivaroxaban at the dose of 15 mg/day in patients with AF was confirmed in several real-life clinical studies, in which there was a lower risk of acute kidney damage and terminal renal failure during the use of DOACs [13, 14].

The creatinine clearance test employing the Cockroft-Gault equation, which is mandatory when administering DOAC, is used in our algorithm for convenience. When selecting rivaroxaban dose, only creatinine clearance is taken into account; no analysis of such factors as age and body weight is required.

For assessing the risk of developing severe coronary complications in patients with AF, the anticoagulant selection algorithm used the 2MACE score developed by Pastori et al. [15] in 2016. Accordingly, in order to stratify the risk, 2 points were allocated in the case of metabolic syndrome and an age of ≥75 years, while 1 point was allocated for myocardial infarction/revascularization, congestive heart failure (ejection fraction ≤40%) or thromboembolism (stroke/transient ischemic attack). A score of 3 or more corresponds to an almost 4 times higher risk of developing severe coronary complications.

Meta-analysis of 28 RCTs showed that the risk of developing myocardial infarction decreases by 22% with the administration of rivaroxaban and increases by 30% with dabigatran [16]. Therefore, it can be argued with confidence that the presence of data for the reduced risk of vascular catastrophes is the criterion for selecting a DOAC [17, 18].

For patients with AF, it is of equal clinical importance to increase treatment compliance and prevent cognitive deficits [3]. Several studies showed that AF caused by a 40–60% decrease in hemodynamics increases the risk of developing cognitive impairments [19–22].

The main mechanisms of developing cognitive deficit during AF are microembolism and brain hypoperfusion [23]. The study findings suggest that the use of DOACs may be accompanied by a reduced risk of developing cognitive deficits in patients with AF, even in cases where the low risk of stroke means anticoagulant therapy is not required. Meanwhile, low time in the target INR range or supratherapeutic INR values are associated in patients taking VKAs with an increased risk of developing dementia. DOACs are superior to VKAs in preventing cognitive deficit, which in turn reduces treatment compliance [24].

A nationwide Dutch study showed that, over a 4-year follow-up period, just over 25% of patients stopped taking DOACs, while the premature withdrawal of anticoagulant therapy was accompanied by the increased risk of stroke by almost 50% and more than double the risk of death [3]. At the same time, a single dose of rivaroxaban was less likely to be prematurely canceled compared to direct anticoagulants with a two-time dosing regimen [25].

This is confirmed by the well-known XANTUS study of routine clinical practice in which 77% of patients had continued taking the drug by the end of the 12-month treatment period and approximately the same number of patients were satisfied with the results of treatment [2, 26].

Rivaroxaban is presented a convenient starter pack with a single-time dosing regimen; a pill can be crushed and mixed with water or other liquid to be taken meals [27].

The drug's DOAC interactions were also studied. The fact that Rivaroxaban does not interact with amiodarone, verapamil or quinidine largely determines its superiority over other DOACs [28].

Conclusion

The presented personalized approach to selecting anticoagulant therapy in atrial fibrillation is based on a comp-

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rehensive decision-making algorithm, which takes into account clinical guidelines, risk assessment of thrombotic and hemorrhagic complications, coronary events, calculation of creatinine clearance, drug interactions, as well as evaluation of treatment compliance.

The decision-making module "Personalized Selection of Anticoagulant in Atrial Fibrillation" was developed to optimize a physician's work by helping to analyze the quality of specialized medical care for each patient and all patients included in the register. Register analysis provides information on the number of patients with tachyarrhythmias taking a particular anticoagulant, evaluates the real-life setting to suggest ways of improving the prognosis and explains the rationale of the guidelines for primary and secondary prevention of acute thrombotic events while minimizing the number of hemorrhagic complications.

The decision-making module can be used by other clinical specialists who prescribe anticoagulants. The analysis of the register of patients with atrial fibrillation supports an assessment of the efficacy of medical care in a single hospital or across an entire region, helps to develop activities for the prevention of complications of anticoagulant therapy and improves the quality and prognosis for life in patients with atrial fibrillation.

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