WHAT SCALES SHOULD THE CARDIOLOGIST USE IN PATIENTS WITH ATRIAL FIBRILLATION? WHAT IS NEW?

DOI: 10.35805/BSK2024II007
Bizhanov K.A.
https://orcid.org/0000-0002-6668-7373
Baimbetov A.K.
https://orcid.org/0000-0003-4553-4287
Baimakhanov B.B.
https://orcid.org/0000-0003-0049-5886
Kaniev Sh.A.
https://orcid.org/0000-0002-1288-0987
Ibekenov O.T.
https://orcid.org/0000-0001-6605-6435
Sarsenbaeva A.B.
https://orcid.org/0000-0002-7890-0047
Ismailova G.N.
https://orcid.org/0000-0002-7461-4190

Bizhanov K.A.[1,2], Baimbetov A.K.[1], Baimakhanov B.B.[1], Kaniev Sh.A.[1], Ibekenov O.T.[1], Sarsenbaeva A.B.[1], Ismailova G.N.[1]

[1]NJSC "Al-Farabi Kazakh National University", Almaty, Kazakhstan
[2]NJSC "S.J. Asfendiyarov Kazakh National Medical University", Almaty, Kazakhstan
[3]NEI "Kazakh-Russian Medical University", Almaty, Kazakhstan

Abstract

The current treatment algorithm for patients with non-valvular atrial fibrillation (AF) includes anticoagulation to prevent stroke and systemic embolism, improvement of AF symptom control by heart rate reduction or restoration and maintenance of sinus rhythm, and treatment of cardiovascular and other comorbidities. The evaluation of patients with AF should be structured and include assessment of stroke risk, symptom severity, severity of the AF burden (type of arrhythmia, number and duration of episodes, etc.) and predisposing condition. The use of the CHA2DS2-VASc (risk of stroke), HAS-BLED (risk of bleeding), EHRA (severity of AF symptoms), and 2MACE (risk of cardiovascular outcomes) scales is important to help assess the likelihood of adverse outcomes and select the optimal treatment to protect not only against stroke but also against cardiovascular events. It should be noted that the HAS-BLED scale is primarily necessary for identification of bleeding risk factors, the modification of which allows to increase the safety of anticoagulant therapy, and a high index value according to this scale can't serve as a reason to refuse anticoagulation in a patient with AF. New scales of stroke and hemorrhagic complications risk assessment in patients with AF on the basis of clinical parameters and laboratory biomarkers have been proposed, but their possible advantages over the existing indices need to be confirmed in special studies.

recieved: 30.04.2024
accepted:19.06.2024

Author for correspondence:
Gulnur Daniyarova
Bizhanov Kenzhebek Alibekovich
kenzhebek10@mail.ru

Conflict of interest:
The authors declare no potential conflict of interest requiring disclosure in this article.

Key words:
Atrial fibrillation, stroke, bleeding, scales, direct oral anyicoagulants, myocardial infarction, interventional arrhythmology, cardiology.

Жүрекшелердің фибрилляциясы бар науқастарда кардиолог қандай таразыларды қолдануы керек? Не жаңалық?

Бижанов Қ.А.[1,2], Баимбетов А.Қ.[3], Баймаханов Б.Б.[2], Қаниев Ш.А.[2], Ибекенов О.Т.[2], Сарсенбаева А.Б.[2], Исмаилова Г.Н.[1]

[1]"Әл-Фараби атындағы Қазақ Ұлттық Университеті", Алматы, Қазақстан
[2]"С.Д. Асфендияров атындағы ҚазҰМУ", Алматы, Қазақстан.
[3]"Қазақстан-ресей Медициналық университеті", Алматы, Қазақстан.

Хаталысатын автор:
Бижанов Кенжебек Алибекович
kenzhebek10@mail.ru

Мүдделер қақтығысы:
авторлар мүдделер қақтығысының жоқтығын мәдімдейді

Түйін сөздер:
Жүрекшелердің фибрилляциясы, инсульт, қан кету, таразылар, тікелей ауызша антикоагулянттар, миокард инфарктісі, интервенциялық аритмология, кардиология.

Тұжырым

Клапандық емес жүрекшелер фибрилляциясы (ЖФ) бар науқастарды емдеудің заманауи алгоритмі инсульт пен жүйелік эмболиялардың алдын алу, жүрек соғу жиілігін төмендету немесе синустық ырғақты қалпына келтіру және ұстап тұру арқылы ЖФ белгілерін бақылауды жақсарту және жүрек-қан тамырлары және басқа да қатар жүретін ауруларды емдеу мақсатында антикоагуляцияны қамтиды. ЖФ-мен ауыратын науқастарды тексеру құрылымды болуы керек және инсульт қаупін, симптомдардың ауырлығын, ЖФ жүктемесінің ауырлығын (аритмия түрі, эпизодтардың саны мен ұзақтығы және т.б.) және бейімділік жағдайын бағалауды қамтуы керек. Cha2ds2-vasc (инсульт қаупі), HAS-BLED (қан кету қаупі), EHRA (ЖФ симптомдарының ауырлығы) және 2MACE (жүрек-қан тамырлары қаупі) шкалаларын қолдану өте маңызды. Бұл қолайсыз нәтижелердің ықтималдығын бағалауға және инсульттан ғана емес, сонымен қатар оңтайлы емдеуді таңдауға көмектеседі. Айта кету керек, HAS-BLED шкаласы ең алдымен қан кету қаупінің факторларын анықтау үшін қажет, олардың модификациясы антикоагулянттық терапияның қауіпсіздігін жақсартуға мүмкіндік береді және осы шкала бойынша жоғары индекс мәні ЖФ бар науқаста антикоагуляциядан бас тартуға негіз бола алмайды. Клиникалық көрсеткіштер мен зертханалық биомаркерлер негізінде ЖФ бар науқастарда инсульт пен геморрагиялық асқынулардың қаупін бағалаудың жаңа шкалалары ұсынылды, бірақ олардың қолданыстағы индекстерден ықтимал артықшылықтары арнайы зерттеулерде растауды қажет етеді.

Какие шкалы должен использовать кардиолог у пациентов с фибрилляцией предсердий? Что нового?

Бижанов К.А.[1,2], Баимбетов А.К.[3], Баймаханов Б.Б.[2], Каниев Ш.А.[2], Ибекенов О.Т.[2], Сарсенбаева А.Б.[2], Исмаилова Г.Н.[1]

Автор для корреспонденции:
Досханов М.О.
Бижанов Кенжебек Алибекович
kenzhebek10@mail.ru

[1]НАО "Казахский Национальный Университет имени Аль-Фараби", Алматы, Казахстан
[2]НАО "Казахский Национальный Медицинский Университет имени С. Д Асфендиярова", Алматы, Казахстан
[3]НУО "Казахстанско-Российский Медицинский Университет", Алматы, Казахстан

Конфликт интересов:
Авторы заявляют об отсутствии конфликта интересов

Ключевые слова:
Фибрилляция предсердий, инсульт, кровотечение, шкалы, прямые пероральные антикоагулянты, инфаркт миокарда, интервенционная аритмология, кардиология.

Аннотация

Современный алгоритм лечения больных с неклапанной фибрилляцией предсердий (ФП) предполагает антикоагуляцию с целью профилактики инсульта и системных эмболий, улучшение контроля симптомов ФП путем урежения частоты сердечных сокращений или восстановления и удержания синусового ритма и лечение сердечно-сосудистых и других сопутствующих заболеваний. Обследование пациентов с ФП должно быть структурированным и включать в себя оценку риска инсульта, выраженности симптомов, тяжести нагрузки ФП (тип аритмии, число и длительность эпизодов и т.п.) и предрасполагающего состояния. Важное значение имеет использование шкал CHA2DS2-VASc (риск инсульта), HAS-BLED (риск кровотече-

ния), шкалы EHRA (выраженность симптомов ФП) и 2MACE (риск сердечно-сосудистых исходов), которые помогают оценить вероятность неблагоприятных исходов и выбрать оптимальное лечение, обеспечивающее защиту не только от инсульта, но и от сердечно-сосудистых событий. Следует отметить, что шкала HAS-BLED в первую очередь необходима для идентификации факторов риска кровотечений, модификация которых позволяет повысить безопасность антикоагулянтной терапии, а высокое значение индекса по этой шкале не может служить основанием для отказа от антикоагуляции у пациента с ФП. Предложены новые шкалы оценки риска инсульта и геморрагических осложнений у больных с ФП на основе клинических показателей и лабораторных биомаркеров, однако их возможные преимущества перед существующими индексами нуждаются в подтверждении в специальных исследованиях.

Management of patients with atrial fibrillation (AF) includes anticoagulation for prevention of stroke and systemic embolism, improvement of AF-related symptoms by rate or rhythm control, and treatment for cardiovascular and other comorbidities. The structured characterization of AF should address four AF-related domains, that is, stroke risk, symptom severity, AF burden (type of AF, number and duration of episodes, etc.), and substrate severity. Various scores, i.e. EHRA (severity of AF-related symptoms), and 2MACE (risk of cardiovascular events), can be used to estimate the risk of outcomes and for treatment decisions. Noteworthy, bleeding risk assessment using HAS-BLED score focuses attention on modifiable risk factors. New clinical and biomarker-based risk scores were developed. However, their potential advantages over existing scores should be confirmed in clinical studies.

The incidence of atrial fibrillation (AF) in the adult population is 2-4% [1]. It increases with age, including due to various comorbidities and risk factors, such as arterial hypertension, diabetes mellitus, coronary heart disease, chronic kidney disease, obesity, alcohol consumption, smoking, etc. In the coming years, we can expect a further increase in the prevalence of AF not only due to increasing life expectancy and aging of the population, but also due to the introduction of new systems for screening of rhythm disorders using mobile technologies (smartphones) that allow registering low-symptomatic or asymptomatic rhythm disorders [2]. For example, in the REHEARSE-AF study, recording of single-lead ECG using a smartphone/tablet twice a week for 12 months in patients aged ≥65 years resulted in a 3.9-fold increase in the rate of AF diagnosis compared with conventional management [3]. The use of such devices for AF screening is most justified in the elderly and elderly, as well as in patients at high risk of stroke [4].

AF is associated with more than 3-fold increase in the risk of death [5] and is one of the main causes of stroke (20-30% and 10% of ischemic and cryptogenic stroke cases, respectively), which is characterized by a severe and recurrent course and often leads to death or disability [1]. AF is accompanied by cardiac dysfunction and the development of heart failure, both with reduced and preserved left ventricular ejection fraction, which is observed in 20-30% of such patients and causes additional deterioration of life prognosis [6]. Adverse effects of AF also include reduced quality of life, especially in women [7], cognitive impairment up to dementia [8], and frequent hospitalizations associated with increased costs to the health care system [9]. According to a meta-analysis of 35 studies, in a total of more than 300,000 patients with AF, the hospitalization rate averaged 43.7 per 100 patients per year, and older age was one of the main factors associated with an increased likelihood of hospitalization [10].

Management of patients with AF

Current approaches to the examination, management and treatment of patients with AF are described in detail in the relevant recommendations of the European Society of Cardiology, which were prepared jointly with the European Association of Cardiothoracic Surgery

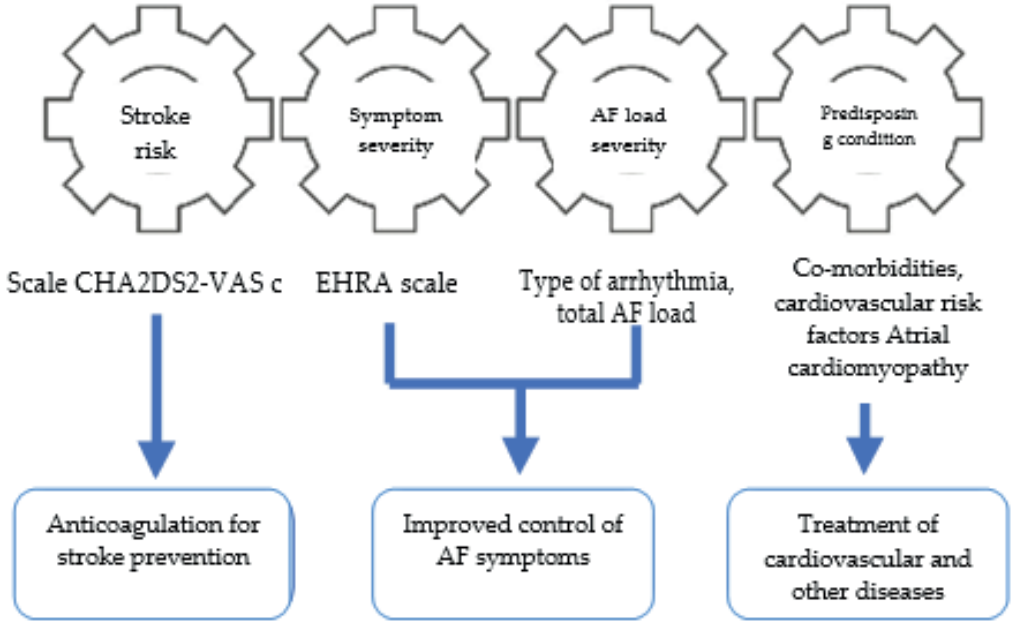

Figure 1.
Shematic of structured examination (4S-AF) and treatment algorithm (ABC) of patients with non-valvular FP

and published in 2020. [11]. These recommendations contain some important innovations, in particular, it was proposed to use a structured scheme of patient examination (4S-AF), involving the analysis of 4 domains (Fig. 1): stroke risk, symptom severity, severity of AF burden, and predisposing condition (AF substrate) [12]. Assessment of the above factors, including using special scales, such as CHA2DS2-VASc, HAS-BLED, EHRA scale, 2MACE, etc., has prognostic value and helps to choose the optimal treatment, which aims not only to provide adequate symptom control and improve quality of life, but also to prevent adverse clinical outcomes, including death. It should be taken into account that the type of AF (first diagnosed, paroxysmal, persistent, long-standing persistent or permanent) is not decisive for the choice of treatment tactics (excluding the question of the need to restore sinus rhythm), for example, to assess the feasibility of oral anticoagulants for the prevention of ischemic stroke.

In order to improve the results of treatment, experts of the European Society of Cardiology recommended using the ABC algorithm, where A - Anticoagulation/Avoid stroke, B - Better symptom management and C - Cardiovascular and Comorbidity optimization (Fig. 1) [13]. The results of clinical trials have shown that implementation of the above algorithm is associated with a reduced risk of death from any cause, cardiovascular events, a combined endpoint including stroke, major bleeding and cardiovascular death, and treatment costs [14-16]. D. Pastori et al. studied the effectiveness of treatment according to the ABC algorithm in preventing cardiovascular complications in a prospective study in 907 patients [17]. In the group of 198 patients who received optimal treatment for about 3 years there was a significant reduction in the risk of any cardiovascular events by 60% (p = 0.003) compared to that in patients in whom at least one component of treatment did not correspond to the optimal one.

Table 1.
CHA2DS2-VASC scale for stroke risk assessment in patients with non-valvular AF [18]

Risk factors	Definition	Score
C	Clinical symptoms of CHF, moderate and severe LV systolic dysfunction (including asymptomatic), hypertrophic cardiomyopathy	1
H	Arterial hypertension (SBP ⩾140 mm Hg, DBP ⩾90 mm Hg) or taking anti-hypertensive medications (target BP for AF 120-129/<80 mm Hg).	1
A	Over 75 years of age	2

D	Type 1 and 2 diabetes mellitus (fasting glycemia more than 7 mmol/l or taking sugar-lowering drugs or insulin therapy)	1
S	History of stroke/TIA/thromboembolism	2
V	History of cardiovascular disease (angiographically confirmed CID, myocardial infarction, clinically significant peripheral atherosclerosis, atherosclerotic plaque in the aorta)	1
A	Age 65-74	1
Sc	Female gender	1

Anticoagulant therapy

The CHA2DS2-VASc scale is used to assess the risk of stroke in patients with atrial fibrillation who require anticoagulant use (Table. 1) [18], which includes congestive heart failure, arterial hypertension, age 275 years, diabetes mellitus, stroke/transient ischemic disease attack/system. embolism in the anamnesis, cardiovascular diseases, including stenosing coronary atherosclerosis, confirmed by angiography, myocardial infarction, atherosclerosis of peripheral arteries or plaques in the aorta, age 65-74 years and women [18]. It should be noted that female gender changes the overall risk of stroke rather than being a risk factor in itself [19], since in the absence of additional risk factors, women have the same low probability of stroke as men, with the CHA2DS2-VASc index equal to 0. At the same time, if there is at least one additional risk factor, the probability of stroke increases in women to a greater extent than in men [20].

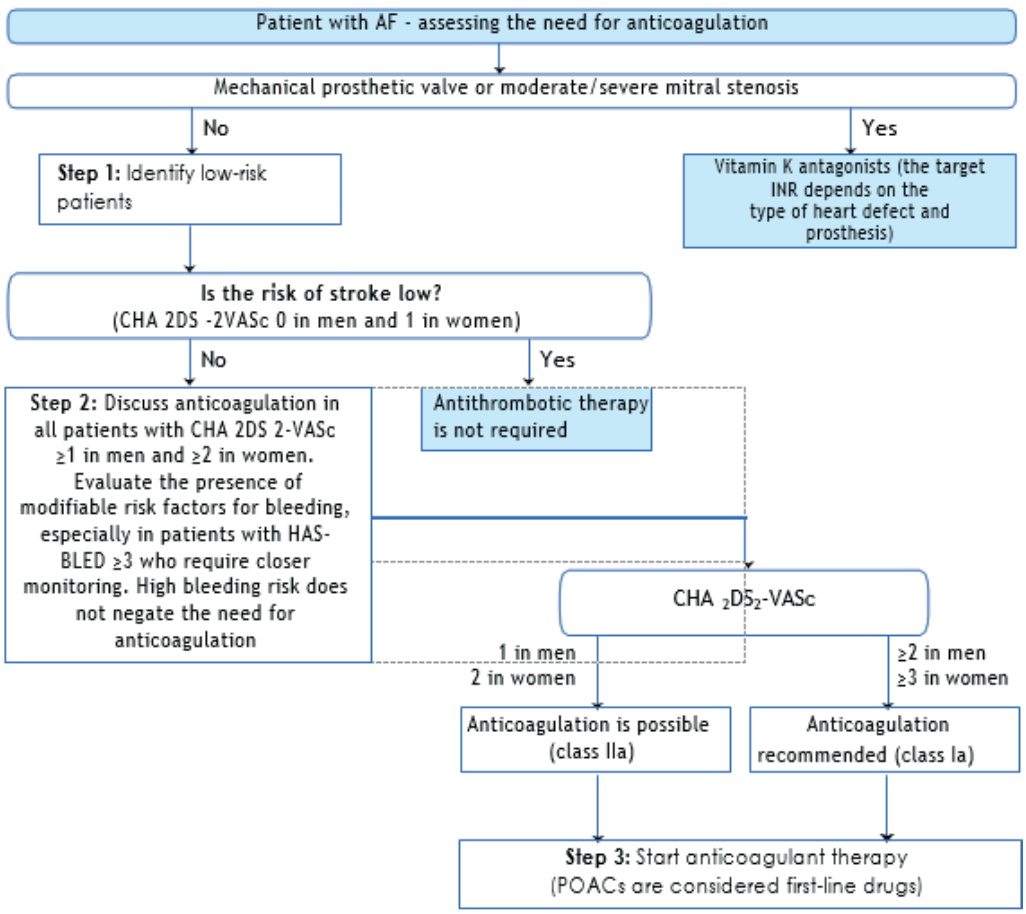

Figure 2.
Anticoagulant therapy in patients with non-valvular AF

In recent years, researchers have shown great interest in studying the role of various biomarkers, including those reflecting myocardial damage (troponin), cardiac dysfunction (natriuretic peptides), myocardial fibrosis (galectin-3),

impaired renal function (creatinine, cystatin C), inflammation (C-reactive protein, cytokines) and coagulant activity II (D-dimer), which may be associated with the pathogenesis of thrombosis, clinical outcomes and treatment effects [21]. The scales of stroke risk assessment in patients with AF are proposed, based not only on clinical risk factors, but also on some laboratory parameters, for example, the ABC scale takes into account the patient's age, the presence of stroke/transient ischemic attack (TIA) in the anamnesis and the levels of highly active sensitive troponin and NT-pro-BNP. The use of some new scales has increased the accuracy of predicting stroke risk in patients with atrial fibrillation, although the practical significance of their possible advantages over the generally accepted scale is small. CHA2DS2-VASc raises doubts, including due to the need for additional costs for the determination of biomarkers. However, it cannot be excluded that the latter they can be used to more accurately assess the likelihood of stroke in patients whose risk of stroke is regarded as low.

Table 2.
HAS-BLED scale for bleeding risk assessment in patients with non-valvular AF [22].

Risk factors	Definition	Score
H	Uncontrolled arterial hypertension (SBP>160 mmHg)	1
A	Renal and/or liver dysfunction (dialysis, kidney transplantation, serum creatinine >200 mmol/l, cirrhosis, bilirubin level more than 2 times the upper limit of normal, AST/ALT/alkaline phosphatase more than 3 times the upper limit of normal)	1*
S	Stroke (ischemic or hemorrhagic stroke)	1
B	Bleeding history or predisposition to bleeding (previous major bleeding, anemia, severe thrombocytopenia)	1
L	Labile INR in patients receiving vitamin K antagonists	1
E	Older age (age>65 years or "frail" patient)	1
D	Concomitant use of medications (antiaggregants and NSAIDs) and/or alcohol (heavy drinking or more than 14 units per week)	1*

Before prescribing oral anticoagulants to patients with AF, it is necessary to assess the risk of bleeding. For this, the HAS-BLED scale is usually used (Table 2). This school retains its importance despite the emergence of new indices, including those that take into account not only clinical and demographic indicators, but also the levels of laboratory biomarkers. For example, the ABC index is calculated taking into account age, a history of bleeding and laboratory biomarkers, including GDF-15, highly sensitive troponin and hemoglobin [22]. The recommendations of the European Society of Cardiology specifically emphasize that there is a high risk of bleeding in the absence of absolute contraindications cannot serve as a reason for refusing anticoagulation therapy, since the "pure" clinical benefit of anticoagulation is even higher in such patients. Risk assessment of hemorrhagic complications is primarily necessary to identify patients who need more careful monitoring (for example, every 4 weeks, not 4-6 months) and modification of risk factors.

Some risk factors for bleeding (age over 65, history of bleeding, renal replacement therapy, malignant tumors, genetic factors, etc.) are unmodified, but many others can be eliminated or reduced (arterial hypertension, concomitant administration of antithrombotic drugs alcohol abuse, anemia, thrombocytopenia, dangerous hobbies, etc.). It should also be taken into account that the change in the risk profile of bleeding in dynamics is of great importance for predicting more severe blood flow than its initial value. In a clinical study, a significant (3.5-fold) increase in the risk of major bleeding over the next 3 months was revealed in patients who had a change in the index on the HAS-BLED scale.

The tendency to fall by itself is not an independent risk factor for bleeding on the background of anticoagulant therapy, however, a fall injury in an elderly patient taking oral anticoagulants can lead to more severe bleeding, for example intracranial. Interesting data were obtained in one study that simulated the effects of falls in patients receiving oral anticoagulants. The authors showed that patients taking warfarin should fall about 295 times a year so that the threat of serious bleeding outweighs the benefit of reducing the risk of ischemic stroke. Nevertheless, these data do not negate the need to prevent falls with simple measures, such as the use of assistive devices when walking, wearing appropriate shoes, removing obstacles for an elderly person in an apartment (carpets, extra furniture).

Indications for the appointment of oral anticoagulants in the new recommendations of the European Society of Cardiology have not changed. Their use is necessary if the index value on the CHA2DS2 scale-VASc is at least 2 in males and 3 in females. This means that oral anticoagulants should be prescribed to all patients with AF (Atrial fibrillation) (regardless of gender) who have reached the age of 75 years, and patients aged 65-74 years in the presence of at least one additional risk factor for stroke, for example, arterial hypertension or diabetes mellitus, while at a younger age the basis for anticoagulation is the presence of at least two risk factors in both men and women (Fig. 2) . If the index on the CHA2DS2-VASc scale is 1 in men or 2 in women, then anticoagulant therapy is considered possible, although clear indications for its appointment in such cases are not given in the recommendations. AF (Atrial fibrillation) usually develops in elderly and senile people suffering from various diseases. Therefore, the index on the CHA2DS2-VASc scale in most patients with this arrhythmia exceeds these values, justifying the use of anticoagulants. In addition, the CHA2DS2-VASc index tends to increase both due to age and the addition of new diseases that increase the risk of stroke. It should be emphasized once again that the type of AF (Atrial fibrillation (paroxysmal/persistent or permanent) does not matter for solving the issue of anticoagulant therapy and is not taken into account when calculating the index on the CHA2DS2-VASc scale.

Vitamin K antagonists, primarily warfarin, or direct oral anticoagulants (OAC), including rivaroxaban, apixaban, dabigatran and edoxaban (the latter is not registered in the Russian Federation) are used to prevent stroke in patients with non-valvular AF. Combined therapy with acetylsalicylic acid and clopidogrel in such patients was inferior in effectiveness to warfarin and was accompanied by a comparable risk of bleeding [24], and monotherapy with acetylsalicylic acid was ineffective and associated with a higher risk of ischemic stroke in elderly people with AF [25]. Thus, antiplatelet drugs should not be considered as a safer alternative to oral anticoagulants in patients with AF who need effective stroke prevention.

Currently, oral anticoagulants (OAC) are considered first-line drugs in stroke prevention in patients with non-valvular AF [11]. In registration clinical trials, all drugs of this group were at least as effective as warfarin. However, a meta-analysis of clinical studies in patients receiving oral anticoagulants revealed a 19% reduction in the risk of stroke and systemic embolism compared to that with warfarin treatment, a 51% reduction in the risk of hemorrhagic stroke and a 10% reduction in the risk of death from any cause. In addition, when using oral anticoagulants (OAC), there was an unreliable decrease in the risk of major bleeding by 14% and a statistically significant decrease in the risk of intracranial bleeding by 52%, while the frequency of gastrointestinal bleeding increased by 25% [26]. These data allow us to consider oral anticoagulants (OAC) as a whole as a more effective and safer alternative to indirect anticoagulants.

Unlike oral anticoagulants (OAC), warfarin can interact with various medications that can enhance or, conversely, weaken its anticoagulant effect. When

treating with indirect anticoagulants, it is necessary to regularly monitor the international normalized ratio (INR) and, if necessary, adjust their doses. In general, vitamin K antagonists are considered effective and relatively safe drugs if the INR can be maintained in the therapeutic range for more than 70% of the time, although this is not always possible. A scale is proposed SAMe-TT2R2 (female, age less than 60 years, presence of at least two concomitant diseases, such as arterial hypertension, diabetes mellitus, coronary artery disease, atherosclerosis of peripheral arteries, heart failure, a history of stroke, lung disease and liver or kidney damage, treatment with certain drugs, smoking, non-European race), which makes it possible to identify patients with AF, in whom it is more difficult to ensure an adequate anticoagulant effect of warfarin [27]. The index value on this scale >2 serves as an additional argument in favor of choosing oral anticoagulants (POAC). If the patient still has to prescribe warfarin or another vitamin K antagonist (usually for economic reasons), then additional measures should be taken to increase the effectiveness and safety of therapy, for example, more frequent monitoring of INR, repeated consultations.

The efficacy profile of oral anticoagulants (OAC) in stroke prevention in patients with non-valvular AF was also confirmed in post-registration studies, the results of which corresponded to those of randomized controlled trials [28-30]. P. Kirchhof et al. the results of the use of rivaroxaban in 11121 patients with non-valvular AF (average age 70.5 ‡ 10.5 years) were summarized; 42.9% of women) included in studies conducted in routine clinical practice in 47 countries under the XANTUS (Xarelto for Prevention of Stroke in Patients with Atrial Fibrillation) program [31]. Prospective research design increases the clinical value of the data obtained. Patients with AF who started taking rivaroxaban were monitored for 1 year. The frequency of major bleeding averaged 1.7 per 100 patient-years, death from any cause - 1.9 per 100 patient-years, stroke and systemic embolism - 1.0 per 100 patient-years. For comparison, the frequency of the primary endpoint, which included stroke and systemic embolism, in the randomized ROCKET AF study, confirmed the effectiveness of rivaroxaban in stroke prevention in patients with non-valvular AF, it was 1.7 per 100 patient-years [32]. The incidence of both bleeding and stroke was low in all countries participating in the XANTUS program, and the proportion of patients who continued taking rivaroxaban during the year was 77.4% (from 66.4% in East Asian countries to 84.4% in Western Europe). The high adherence to anticoagulant therapy reflects the convenience of using rivaroxaban, including the absence of the need for dose titration and regular monitoring of INR, the low risk of interaction with other drugs, the stability of the anticoagulant effect and the possibility of prescribing once a day.

All DOACs are partially eliminated by the kidneys, dabigatran to a greater extent and rivaroxaban and apixaban to a lesser extent, so renal function should be taken into account when choosing a drug and its dose. For example, the dose of rivaroxaban in patients with creatinine clearance15-49 ml/min should be reduced from 20 to 15 mg once daily. To ensure the safety of anticoagulant therapy in patients with atrial fibrillation, it is necessary to regularly monitor renal function using creatinine clearance calculated using the Cockcroft-Gold formula, since this is the indicator used in registration clinical studies. Renal function should be assessed at least once a year, or more frequently in patients at risk, such as those with baseline decreased renal function. In patients with impaired and/or deteriorating renal function, it is advisable to consider the use of oral anticoagulants, which are less excreted by the kidneys (rivaroxaban or apixaban).

The practice guideline of the European Association of Arrhythmology recommends measuring creatinine clearance every 6 months in patients aged >75 years (especially when treated with dabigatran) and "frail" patients. To estimate the minimum interval for determining

creatinine clearance in patients with initially reduced renal function, creatinine clearance should be divided by 10. For example, in patients with a value of 40 ml/min, creatinine clearance should be measured at least every 4 months. It must be taken into account that renal function can quickly deteriorate under the influence of various intercurrent diseases, for example, infections or acute heart failure. Accordingly, in such cases it is also necessary to measure creatinine clearance.

Atrial fibrillation in approximately a third of cases is combined with stage II-V chronic kidney disease (CKD), a decrease in the estimated glomerular filtration rate (GFR)<60 ml/min/1.73 m, which reflects the commonality of risk factors for the two conditions, such as old age, arterial hypertension, diabetes mellitus, etc. Moreover, approximately every fourth elderly patient with non-valvular atrial fibrillation can be expected to experience progression of CKD. For example, in the ORBIT-AF II study in 6682 patients with atrial fibrillation (median age 72 years) receiving DOACs or warfarin, the incidence of creatinine clearance decreases of more than 20% and 30% at 1 year of follow-up was 23.1 % and 10.6%, respectively. The combination of non-valvular AF with CKD is associated with an additional increase in the risk of ischemic stroke, bleeding and other adverse outcomes. In registration studies of DOACs, more than half of the patients had evidence of renal impairment. According to a meta-analysis of 4 randomized clinical trials ROCK-ET-AE, RE-LY, ARISTOTLE and ENGAGE AF-TIMI 48, which studied rivaroxaban, dabigatran, apixaban and edoxaban, accordingly, during the treatment of DOACs in patients with AF and impaired renal function, a significant reduction in the relative risk of stroke and systemic embolism was noted by 20% (p <0.01), major bleeding by 21% (p = 0.017) and death from any cause by 9% (p = 0.031) compared with that with warfarin.

Moreover, the "net" benefit of DOACs, which was assessed taking into account the risk of not only stroke/systemic embolism, but also bleeding, increased as renal function worsened and was highest in patients with creatinine clearance 30-50 ml/min. In the ROCKET AF study, progression of CKD, the criterion of which was a decrease in creatinine clearance by more than 20% compared to baseline, was detected in 26.3% of patients. Worsening renal function was associated with an increased risk of death from vascular causes, a composite endpoint of stroke, systemic embolism, cardiovascular death and myocardial infarction, and death from any cause compared with that in patients with stable renal function. Treatment with rivaroxaban compared with warfarin in patients with advanced CKD resulted in a reduced risk of stroke and systemic embolism and did not increase the risk of major and clinically significant minor bleeding.

Retrospective studies have shown that DOAC treatment in patients with non-valvular AF may be associated with improved renal outcomes compared with warfarin, including a reduction in the incidence of acute kidney injury (AKI) associated with nephropathy due to over-anticoagulation and glomerular hemorrhage. In a retrospective study, the incidence of warfarin-associated AKI was 33.0% in patients with CKD and 16.5% in patients with normal renal function. Treatment with DOACs can be expected to reduce the risk of AKI due to a more predictable anticoagulant effect compared to warfarin. C. Coleman et al. analyzed renal outcomes in a retrospective study of 72,000 patients with AF who started treatment with rivaroxaban or warfarin at for at least 12 months.

In another retrospective study, renal outcomes were assessed in 9769 patients with nonvalvular AF treated with various DOACs or warfarin. Treatment with DOACs for 2 years was associated with a significant reduction in the risk of developing or progressing CKD, in particular the likelihood of a reduction in GFR by at least 30% (odds ratio 0.77; 95% CI 0.66-0.89; p < 0.001) and doubling of serum creatinine (0.62; 0.40-0.95; p = 0.03) compared with that during treatment with warfarin. Improved renal

prognosis was found with rivaroxaban and dabigatran, but not with apixaban. This benefit of rivaroxaban may support its preferential use in patients with deteriorating renal function.

Improved symptom control

To assess the symptoms (palpitations, shortness of breath, fatigue, chest discomfort, etc.), AF uses a scale proposed by the European Association of Arrhythmologists (EHRA) and reflecting the effect of arrhythmia manifestations on the usual daily activity of patients (Table. 3) [46, 47]. It should be borne in mind that all these symptoms are nonspecific and may be the result of concomitant diseases, and it is sometimes possible to confirm their connection with AF only retrospectively. In the recommendations of the European Society of Cardiology, it is also proposed to assess the severity of the AF load, which reflects its type, the total duration of the rhythm disturbance during ECG monitoring, for example, for 24 hours, the number of arrhythmia episodes, their maximum duration, etc. [11]. It should be noted that the recommendations lack clear criteria for interpreting the data obtained. In some studies, an association was found between the parameters of the FTP load and adverse clinical outcomes. A. Ganesan et al. in a meta-analysis of 12 studies in approximately 100,000 patients with non-paroxysmal non-valvular AF revealed an increased risk of thromboembolism and death (relative risk 1.384; p <0.001, and 1.217, p <0.001, respectively) compared with that in patients with paroxysmal AF [39]. The load of AF may have a certain effect on the effectiveness of rhythm control in patients with VP [40]. Nevertheless, according to experts, the available data on the relationship of the load of AF with clinical outcomes are insufficient to give them decisive importance when choosing a treatment strategy.

The heart rate (HR) control strategy in patients with non-valvular AF was as effective in preventing adverse outcomes as the sinus rhythm control strategy and often proves to be sufficient to reduce symptoms, especially in elderly patients [11]. Research results RACE II showed that more "rigid" heart rate control, which assumed a decrease of <80 per minute at rest and <110 per minute with moderate physical activity, does not lead to a decrease in the overall risk of clinical outcomes [41]. In this regard, the target value of the resting heart rate when choosing a heart rate control strategy may be <110 per minute, although the goal of therapy may be revised if symptoms persist or left ventricular function worsens.

Table 3.
Scale for assessing the severity of AF symptoms (EHRA) [11]

EHRA Class	Symptoms	Description
1	absent	AF is not accompanied by any symptoms
2a	mild	AF symptoms do not affect normal daily activity
2b	moderate	Symptoms of AF do not affect normal daily activity, but cause anxiety in the patient
3	pronounced	Symptoms of AF disrupt normal daily activity
4	disabling	Normal daily activity is impossible

To control heart rate in patients with non-valvular AF, P-blockers are usually used, as well as digoxin, diltiazem and verapamil or a combination of these drugs, while antiarrhythmic agents such as amiodarone or sotalol are better prescribed to control sinus rhythm. Treatment usually begins with beta-blockers, although in the presence of chronic obstructive pulmonary disease or bronchial asthma, the advantages of non-dihydropyridine calcium antagonists are obvious. At the same time, the latter should not be prescribed to patients with a left ventricular ejection fraction < 40%. If combination therapy with drugs that reduce the heart rate is ineffective, atrioventricular node ablation can be performed in combination with implantation of an artificial pacemaker.

As mentioned above, a rhythm control strategy involving the restoration and retention of the blue rhythm does not improve clinical outcomes in patients with AF, therefore, its primary goal is to reduce symptoms and improve the quality of life of patients. The restoration of the sinus rhythm does not mean that there is no need to take medications that reduce heart rate, anticoagulation and correction of cardiovascular risk factors.

Control of the sinus rhythm can prevent the progression of AF, i.e. its transition to a more stable form, for example, the transformation of paroxysmal AF into persistent or permanent or persistent AF into a permanent form. In an American cohort study in 955 patients with newly diagnosed non-valvular AF, the rate of arrhythmia progression for 12 months against the background of sinus rhythm control was significantly lower than against the background of heart rate control (5.8% and 27.6%, respectively; p <0.001). The progression of AF was also associated with old age, the presence of persistent AF and stroke/TIA in anamnesis. The arguments in favor of choosing a sinus rhythm control strategy may be the following:

- younger age of the patient;
- the first episode of AF or a short history;
- cardiomyopathy caused by tachycardia;
- absence of pronounced dilatation of the left atrium;
- absence of heart disease or concomitant diseases;
- difficulties in heart rate control;
- transient cause of AF, for example, acute illness;
- the patient's desire.

Methods of monitoring the sinus rhythm after its restoration by electrical or medical cardioversion in patients with paroxysmal or persistent AF include the use of antiarrhythmic drugs and catheter ablation. The latter is considered an effective and safe method, although in the CABANA study catheter ablation did not significantly reduce the risk of a combined endpoint, which included death, disabling stroke, serious bleeding and cardiac arrest, compared with drug therapy, but was accompanied by a significant improvement in the quality of life. Catheter ablation is usually performed when at least one class I or III antiarrhythmic drug is ineffective or poorly tolerated, although it can also be considered as a first-line method in patients with paroxysmal AF or patients with persistent AF who lack the main factors of arrhythmia recurrence after intervention (such as age, left atrium dilation, duration of AF, impaired renal function, etc.) [11]. In addition, catheter ablation is recommended to restore the function of the left ventricle in patients with cardiomyopathy induced by tachycardia, and to increase survival and reduce the frequency of hospitalizations in patients with heart failure and reduced left ventricular function. At least one third of patients who have undergone catheter ablation have relapses of AF at various times after the intervention. Currently, various scales have been proposed to assess the risk of recurrence of arrhythmia after catheter ablation, including ALARMEc (type of arrhythmia, left atrium size, renal failure, metabolic syndrome and cardiomyopathy), BASE-AF2 (body mass index > 28 kg/m2, left atrium dilation >40 mm, early recurrence of AF after ablation, duration of AF >6 years and non-paroxysmal form of arrhythmia), APPLE (age ≥65 years, persistent AF, decreased glomerular filtration rate <60 ml/min/1.73 m", left atrium diameter 243 mm and left ventricular ejection fraction <50%), CAAP-AF (coronary heart disease, left atrium diameter, age, persistent or prolonged AF, ineffectiveness of antiarrhythmic drugs and female gender), ATLAS (age over 60 years, non-paroxysmal AF, left atrial dilatation, female sex and smoking), but none of them had significant advantages over the others [42]. Modification of various risk factors, including smoking, alcohol consumption, arterial hypertension, obesity, etc., may contribute to improving the results of catheter ablation in patients with non-valvular AF.

The recommendations of the European Society of Cardiology highlight

the following principles of antiarrhythmic therapy in patients with non-valvular AF:

• The purpose of antiarrhythmic therapy is to reduce the symptoms associated with AF.

• Antiarrhythmic therapy is characterized by moderate effectiveness in the prevention of AF relapses.

• Antiarrhythmic therapy reduces the number of recurrent arrhythmias rather than completely prevents them.

• If one antiarrhythmic drug is ineffective, then an acceptable clinical effect can be achieved with the help of another drug.

• Antiarrhythmic therapy is often accompanied by an arrhythmogenic effect and extracardial side effects.

• The choice of an antiarrhythmic drug is primarily dictated by safety, not effectiveness.

Amiodarone remains the most effective antiarrhythmic drug in patients with AF, including those with heart failure and low left ventricular ejection fraction. The recommendations indicate that, taking into account the extracardial toxicity of amiodarone, it is desirable to use other antiarrhythmic drugs, if possible, for longterm control of sinus rhythm in patients with AF [11]. However, as in previous versions of the recommendations, other antiarrhythmic agents, such as propafenone and sotalol, are recommended to be used only in the absence of signs of significant structural damage to the heart. Sotalol can be used in patients with coronary heart disease under careful monitoring of the QT interval, serum potassium levels, creatinine clearance and other risk factors for arrhythmogenic effects. The latter include old age, female gender, impaired kidney and/or liver function, coronary heart disease, hypokalemia, cases of sudden death in relatives. Antiarrhythmic therapy should not be prescribed to patients with a permanent form of AF who receive rhythm reducing drugs, as well as to patients with severe conduction disorders if they do not have a rhythm driver installed.

Table 4.
Scale 2 MASE, designed to assess the risk of cardiovascular events in patients with non-valvular AF [11]

Acronym	Risk factors	Score
2M	Myocardial infarction/coronary artery revascularization in anamnesis	1
	Metabolic syndrome	2
A	Age >75 years	2
C	Congestive heart failure (ejection fraction<40%)	1
E	Thromboembolism	1

Treatment of cardiovascular Vascular and other related diseases

Cardiovascular diseases and risk factors, on the one hand, contribute to the development and recurrence of atrial fibrillation, and, on the other hand, they themselves can cause adverse outcomes, including stroke, heart attack and death. A. Gómez-Outes et al. conducted a meta-analysis of 4 clinical trials in which direct, oral anticoagulants compared with warfarin in general in 71683 patients with non-valvular atrial fibrillation [33]. During the follow-up period, 9% of them died, and the adjusted mortality rate was 4.72% per year. The share of cardiac causes in the structure of total mortality was 46%. The main risk factors for death from any cause were heart failure, persistent/persistent atrial fibrillation, diabetes mellitus, male gender, old age and reduced creatinine clearance. Similar data were obtained in one of the studies included in the meta-analysis, ROCKET AF, in which rivaroxaban was studied [34]. These data indicate the importance of modifying cardiovascular risk factors to improve the prognosis in patients with non-valvular atrial fibrillation. Scales are proposed that allow stratifying patients with non-valvular atrial fibrillation by the risk of major cardiovascular events, including fatal and non-fatal myocardial infarction, coronary artery revascularization and death from cardiovascular causes. for example, based on a prospective cohort study in 1019 patients with atrial fibrillation,

a 2MASE index was developed, which is calculated taking into account age and the presence of metabolic syndrome, congestive heart failure and myocardial infarction/revascularization of the core-carotid arteries and thromboembolism in the anamnesis (Table. 4). The value of the 2MASE index varies from 0 to 7, and its value ⩾3 allowed predicting the development of unfavorable outcomes with high sensitivity and specificity in patients with non-valvular atrial fibrillation (risk ratio 3.92, 95% CI 2.41-6.40, p <0.001).

Treatment of concomitant diseases and modification of cardiovascular risk factors are considered as one of the key components of the modern management strategy for patients with atrial fibrillation [11]. In a randomized RACE trial 3 more "aggressive" treatment of concomitant cardiovascular diseases led to a significant increase in the frequency of sinus rhythm retention compared with conventional therapy (75% and 63%, respectively, p = 0.042) [11]. Some studies have studied the effect of modification of individual risk factors on the course of atrial fibrillation. In a randomized study in 184 patients with atrial fibrillation who underwent catheter ablation, more "aggressive" antihypertensive therapy did not cause a decrease in the risk of arrhythmia recurrence after the intervention, but was accompanied by an increase in the frequency of episodes of arterial hypotension. At the same time, optimal glycemic control for 12 months prior to catheter ablation was associated with a reduced risk of arrhythmia recurrence. In another randomized clinical trial, abstinence caused a decrease in the frequency of episodes of atrial fibrillation in patients who regularly consumed alcohol [35]. On the other hand, caffeine probably does not significantly affect the risk of atrial fibrillation, although coffee consumption may be accompanied by palpitations unrelated to arrhythmia [36]. Regular moderate physical activity can have a beneficial effect on the course of atrial fibrillation, while intense physical activity, on the contrary, is associated with an increased risk of its development [37]. Weight loss in obese patients and atrial fibrillation caused a decrease in symptoms and frequency of arrhythmia attacks [38]. In general, the results of modification of individual risk factors in clinical trials in patients with atrial fibrillation oca- became ambiguous. This is probably due to the fact that the development of atrial fibrillation is a consequence of the interaction of various cardiovascular and other risk factors and diseases.

Atrial fibrillation is often observed in patients with acute and chronic coronary syndrome, and approximately 10-15% of patients with atrial fibrillation have percutaneous interventions on the coronary arteries (Percutaneous coronary interventions) [39]. Medications that are used to treat coronary heart disease, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, statins, may interfere with the development of atrial fibrillation or have a beneficial effect on its course, while beta-blockers or non-dihydropyridine antagonists Calcium compounds are widely used in patients with atrial fibrillation to control heart rate. However, the possibility and feasibility of combination therapy with oral anticoagulants and antiplatelet drugs in patients with coronary heart disease and atrial fibrillation deserves a separate discussion, considering the significant increase in the risk of bleeding on the background of such treatment. The recommendations of the European Society of Cardiology indicate that when choosing antithrombotic drugs and the duration of antithrombotic therapy in patients with non-valvular atrial fibrillation who have undergone acute coronary syndrome (Acute coronary syndromes) and/or Percutaneous coronary interventions, it is necessary to carefully weigh the risk of ischemic stroke/systemic embolism, coronary ischemic complications and blood-currents associated with taking anti-thrombotic drugs [11]. In general, therapy with two antithrombotic drugs, including direct, oral anticoagulants and a P2U12 receptor inhibitor (preferably clopidogrel) was accompanied by a sig-

nificant reduction in the risk of bleeding compared with triple antithrombotic therapy. For example, the PIONEER AF-PCI study included 2124 patients with non-valvular atrial fibrillation who underwent coronary artery stenting (in half of cases for acute coronary syndromes), rivaroxaban therapy at a reduced dose of 15 mg once a day (in patients with impaired renal function, it was reduced to 10 mg/day) in combination with a P2Y12 receptor inhibitor (mainly clopidogrel) for 12 months according to its effectiveness in preventing unfavorable outcomes, including myocardial infarction, stroke, stent thrombosis and death from cardiovascular causes, It was not inferior to vitamin K antagonist therapy in combination with two antiplatelet drugs, but was accompanied by a significant reduction in the risk of clinically significant bleeding by 41% [40]. Nevertheless, experts of the European Society of Cardiology consider desirable a short course of triple antithrombotic therapy with oral anticoagulant, aspirin and clopidogrel (for example, for 51 weeks) in some patients with atrial Fibrillation who have undergone Acute coronary syndromes or Percutaneous coronary interventions, who have a high risk of ischemic complications [11]. The duration of triple therapy can be increased to < 1 month if the threat of stent thrombosis outweighs the risk of bleeding. Risk factors for thrombotic complications include diabetes mellitus, a history of acute coronary syndromes, damage to several coronary arteries, atherosclerosis of peripheral arteries, the development of coronary disease under the age of 45 or its rapid progression, chronic kidney disease of stage 3 [11].

Dual therapy with direct, oral anticoagulants and clopidogrel after uncomplicated coronary artery stenting in patients with acute coronary syndromes is usually continued for 1 year, and in patients with stable chronic coronary artery disease who have undergone percutaneous coronary interventions - for 6 months. If no ischemic complications were registered during the specified period, then in the future it is advisable to carry out monotherapy with an oral anticoagulant. Monotherapy is also recommended for patients with non-valvular atrial fibrillation and stable ischemic heart disease.

The arguments in favor of monotherapy with oral anticoagulants are, on the one hand, their supposed effectiveness in the prevention of cardiovascular events, and, on the other hand, a lower risk of bleeding, which inevitably increases with the addition of additional anti-thrombotic drugs. R. Kir et al. a meta-analysis of 28 randomized clinical trials was conducted, in which direct, oral anticoagulants were compared with vitamin K antagonists, antiplatelet drugs and/or placebo for various indications in a total of 196761 patients [43]. Treatment with rivaroxaban was associated with a reduction in the relative risk of myocardial infarction by 21% compared with placebo and by 31% compared with dabigatran. Similar data were previously obtained by other authors. For example, Y. Loke et al. a meta-analysis of 27 randomized controlled clinical trials revealed a reduction in the risk of coronary complications with the use of rivaroxaban compared with that with the treatment of dabigatran [44]. When interpreting the data obtained, it should be taken into account that direct, oral anticoagulants were not obtained in direct comparative studies, and indications for their use included not only non-valvular atrial fibrillation, but also other conditions.

Limitations

There were no significant limitations during research

Conclusion

The modern strategy for the treatment of patients with non-valvular AF, which is discussed in detail in the recommendations of the European Society of Cardiology 2020, involves anticoagulation for the prevention of stroke and systemic embolism, improving the control of AF symptoms by reducing heart rate or restoring and maintaining sinus rhythm and optimal treatment of cardiovascular and other concomitant diseases that are in the structure of mortality of patients with AF they occupy an even

more important place than ischemic stroke. Data are accumulating demonstrating additional advantages of POAC (Primary Options for Acute Care) over indirect anticoagulants. For example, meta-analyses of randomized clinical trials have shown a reduction in the risk of myocardial infarction/acute coronary syndrome when treated with rivaroxaban compared with controls. In retrospective studies, treatment with rivaroxaban improved renal outcomes in patients with non-valvular AF. Patients with AF should undergo a structured examination, including an assessment of the risk of stroke, the severity of symptoms, the severity of the load of AF (type of arrhythmia, number and duration of episodes, etc.) and predisposing condition. It is important to use various scales, including CHA2DS2-VASc (risk of stroke), HAS-BLED (risk of bleeding), EHRA scale (severity of AF symptoms) and 2MACE (risk of cardiovascular outcomes), which help to choose the optimal treatment. For a more accurate assessment of the risk of stroke and bleeding in patients with AF, new scales have been proposed based not only on clinical indicators, but also on laboratory markers, but their potential advantages over existing generally accepted indices need to be confirmed.

Acknowledgment: The authors would like to express their sincere appreciation to the Library Fund and the staff of the institutional scientific libraries.

Authors' Contributions: B.K., B.A., B.B., K.Sh.: Study conception and design, revising discussion section of the manuscript. B.K., I.O., S.A.: Study design, data analysis, and interpretation, revising discussion section of the manuscript. B.K., G.N., S.A.: Data acquisition, analysis, and interpretation. B.K., S.A.: Data collection, drafting, revising results section. All authors have approved the final version of the article.

Funding: none

References

1. Benjamin EJ, Muntner P, Alonso A, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2019 update: a report from the American Heart Association. Circulation 2019;139:e56-528.

2. Li KHC, White FA, Tipoe T, et al. The current state of mobile phone apps for monitoring heart rate, heart rate variability, and atrial fibrillation: narrative review. JMIR Mhealth Uhealth 2019;7:e11606.

3. Halcox JPJ, Wareham K, Cardew A, Gilmore M, et al. Assessment of remote heart rhythm sampling using the AliveCor heart monitor to screen for atrial fibrillation: the REHEARSE-AF Study. Circulation 2017;136:1784-94.

4. Freedman B, Camm J, Calkins H, et al, SCREEN CollaboratorsAF. Screening for atrial fibrillation: a report of the AF- SCREEN International Collaboration. Circulation 2017;135:1851-67.

5. Magnussen C, Niiranen TJ, Ojeda FM, et al, BiomarCaRE Consortium. Sex dif- ferences and similarities in atrial fibrillation epidemiology, risk factors, and mor- tality in community cohorts: results from the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation 2017;136: 1588-97.

6. Kotecha D, Lam CS, Van Veldhuisen DJ, et al. Heart failure with preserved ejec- tion fraction and atrial fibrillation: vicious twins. J Am Coll Cardiol 2016;68:2217- 28.

7. Blum S, Muff C, Aeschbacher S, et al. Prospective assessment of sex-related dif- ferences in symptom status and health perception among patients with atrial fibril- lation. J Am Heart Assoc 2017;6:e005401.

8. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associat- ed with atrial fibrillation: a meta-analysis. Ann Intern Med 2013;158:338-46.

9. Kim MH, Johnston SS, Chu BC, Dalal MR, Schulman KL. Estimation of total incremental health care costs in patients with atrial fibrillation in the

United States. Circ Cardiovasc Qual Outcomes 2011;4:313-20.

10. Meyre P, Blum S, Berger S, et al. Risk of hospital admissions in patients with atrial fibrillation: a systematic review and meta- analysis. Can J Cardiol 2019;35:1332- 43.

11. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS) [published online ahead of print, 2020 Aug 29]. Eur Heart J. 2020;ehaa612. doi:10.1093/eur- heartj/ehaa612.

12. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF scheme (Stroke Risk; Symptoms; Severity of Burden; Substrate): A novel approach to in-depth characterization (rather than Classification) of atrial fibrillation. Thromb Haemost 2020; doi: 10.1055/s-0040-1716408.

13. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017;14:627-28.

14. Proietti M, Romiti GF, Olshansky B, et al. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) Pathway. Am J Med 2018;131:1359-1366.

15. Yoon M, Yang PS, Jang E, et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. Thromb Haemost 2019;19:1695-703.

16. Pastori D, Farcomeni A, Pignatelli P, et al. ABC (Atrial fibrillation Better Care) pathway and healthcare costs in atrial fibrillation: the ATHEROAF study. Am J Med 2019;132:856-61.

17. Pastori D, Pignatelli P, Menichelli D, et al. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events: the ABC (Atrial fibrillation Better Care) pathway in the ATHERO-AF study cohort. Mayo Clin Proc 2019;94:1261-67

18. Predictive value of CHA2DS2-VASc scores regarding the risk of stroke and all-cause mortality in patients with atrial fibrillation (CONSORT compliant) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708930/ Table 1.

19.Wu VC, Wu M, Aboyans V, et al. Female sex as a risk factor for ischaemic stroke varies with age in patients with atrial fibrillation. Heart 2020;106:534-40.

20.Nielsen PB, Skjoth F, Overvad TF, et al. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation 2018;137:832-40.

21.Hijazi Z, Oldgren J, Siegbahn A, Wallentin L. Application of biomarkers for risk stratification in patients with atrial fibrillation. Clin Chem 2017;63:152-64.

22.Borre ED, Goode A, Raitz G, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. Thromb Haemost 2018;118:2171-87.

23. https://www.chil.kz/Aux/Edition-Download/166 Man-Medicine Kazakhstan, №10 (154) Cardiology, rheumatology, page 25, figure 2.

24.ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of VascularEvents (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.

25.Sjalander S, Sjalander A, Svensson PJ, Friberg L. Atrial fibrillation patients do not benefit from acetylsalicylic acid. Europace 2014;16:631-8.

28.Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. Chest 2013;144:1555-63.

29.Camm AJ, Amarenco P, Haas S, et al; XANTUS Investigators. XANTUS: a real- world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2016;37:1145-53.

30.Martinez CAA, Lanas F, Radaideh

G, et al; XANTUS Investigators. XANTUS- EL: a real-world, prospective, observational study of patients treated with rivarox- aban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. Egypt Heart J 2018;70:307-13.

33.Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in 'real-world' clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost 2017;117:1072- 82.

31.Kirchhof P, Radaideh G, Kim Y-H, et al. Global prospective safety analysis of rivaroxaban. J Am Coll Cardiol 2018;72:141-53.

32.Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvu- lar atrial fibrillation. N Engl J Med 2011;365:883-91.

33. Gómez-Outes A, Lagunar-Ruíz J, Terleira-Fernández AI, Calvo-Rojas G, Suárez-Gea ML, Vargas-Castrillón E. Causes of Death in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2016 Dec 13;68(23):2508-2521. doi: 10.1016/j.jacc.2016.09.944. PMID: 27931607.

34. Monga T S, Ekong M, Patrick K, et al. (June 03, 2024) Anticoagulation in Atrial Fibrillation Associated With Cardiac Amyloidosis: A Narrative Review. Cureus 16(6): e61557. doi:10.7759/cureus.61557

35. Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM. Alcohol Abstinence in Drinkers with Atrial Fibrillation. N Engl J Med. 2020 Jan 2;382(1):20-28. doi: 10.1056/NEJMoa1817591. PMID: 31893513.

36. Surma S, Romańczyk M, Filipiak KJ, Lip GYH. Coffee and cardiac arrhythmias: Up-date review of the literature and clinical studies. Cardiol J. 2023;30(4):654-667. doi: 10.5603/CJ.a2022.0068. Epub 2022 Aug 1. PMID: 35912715; PMCID: PMC10508080.

37. Tatangelo M, Rebecchi M, Sgueglia M, Colella A, Crescenzi C, Panattoni G, Ciampi P, Lanza O, Canali E, Calò L. The Complex but Fascinating Relationship between Sport and Atrial Fibrillation: From Pathophysiology to the Clinical Scenario. Journal of Cardiovascular Development and Disease. 2023; 10(6):255. https://doi.org/10.3390/jcdd10060255

38. Ahammed MR, Ananya FN. Impact of Weight Loss on Atrial Fibrillation. Cureus. 2023 Sep 29;15(9):e46232. doi: 10.7759/cureus.46232. PMID: 37908920; PMCID: PMC10614082.

39. Hamaguchi T, Iwanaga Y, Nakai M, Morita Y, Inoko M. Clinical Significance of Atrial Fibrillation Status in Patients With Percutaneous Coronary Intervention. CJC Open. 2021 Jul 6;3(11):1357-1364. doi: 10.1016/j.cjco.2021.06.018. PMID: 34901804; PMCID: PMC8640652.

40. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375(25):2423-34

41. Van Gelder IC, Groenveld HF, Crijns HJ, et al.; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010;362:1363-73.

42. Kosich F, Schumacher K, Potpara T, et al. Clinical scores used for the prediction of negative events in patients undergoing catheter ablation for atrial fibrillation. Clin Cardiol 2019;42:320-9.

43. Kupó P, Szakács Z, Solymár M, et al. Direct anticoagulants and risk of myocardial infarction, a multiple treatment network meta-analysis. Angiology 2020;71: 27-37.

44. Loke YK, Pradhan S, Yeong JK, Kwok CS. Comparative coronary risks of apixaban, rivaroxaban and dabigatran: a meta-analysis and adjusted indirect comparison. Br J Clin Pharmacol 2014;78:707-17.