DOI: https://doi.org/10.17816/cardar321821

Review article

Features of the use of oral anticoagulants in clinical practice: focus on gastrointestinal complications

Natalya V. Bakulina, Sergey V. Tikhonov, Anna G. Apresyan, Inna G. Ilyashevich

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

The review article presents dates about the physiology and pathophysiology of the hemostasis system, discusses the features of the use of oral anticoagulants in clinical practice. Oral anticoagulants are drugs characterized by predictable pharmacokinetics and pharmacodynamics, a favorable efficacy and safety profile. The article considers the main clinical and pharmacological characteristics of apixaban, rivaroxaban and dabigatran (bioavailability, metabolism, excretion); factors that increase the risk of gastrointestinal bleeding associated with anticoagulant therapy; drug interactions; the possibility of gastroprotection in patients taking oral anticoagulants. In real clinical practice, the reason for not prescribing or unreasonably reducing the dose of oral anticoagulants is the fear of bleeding. In this case, the risks of bleeding, as a rule, are overestimated. Knowledge of bleeding risk factors, prognostic scales and management of risk factors is an approach that can improve the safety of anticoagulant therapy. In clinical practice, the choice of the ideal oral anticoagulants, in addition to taking into account the risk of bleeding, should be based on a comprehensive assessment, including an assessment of the patient's age, risk of stroke and coronary events, renal function, and predicted compliance.

Keywords: apixaban; rivaroxaban; dabigatran; pharmacokinetics; bioavailability; adverse drug reactions; gastrointestinal bleeding.

To cite this article:
Bakulina NV, Tikhonov SV, Apresyan AG, Ilyashevich IG. Features of the use of oral anticoagulants in clinical practice: focus on gastrointestinal complications. *Cardiac Arrhythmias*. 2023;3(2):29–40. DOI: https://doi.org/10.17816/cardar321821

Received: 20.05.2023 **Accepted:** 12.07.2023 **Published:** 31.07.2023

All rights reserved
© Eco-Vector, 2023

DOI: https://doi.org/10.17816/cardar321821

Обзорная статья

Особенности применения пероральных антикоагулянтов в клинической практике: фокус на желудочно-кишечные осложнения

Н.В. Бакулина, С.В. Тихонов, А.Г. Апресян, И.Г. Ильяшевич

Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

В обзорной статье представлены данные о физиологии и патофизиологии системы гемостаза, обсуждаются особенности применения прямых пероральных антикоагулянтов (ПОАК) в клинической практике. ПОАК – препараты, характеризующиеся прогнозируемой фармакокинетикой и фармакодинамикой, благоприятным профилем эффективности и безопасности. В статье рассмотрены основные клинико-фармакологические характеристики апиксабана, ривароксабана и дабигатрана (биодоступность, метаболизм, выведение); факторы, повышающие риск желудочно-кишечных кровотечений, ассоциированных с антикоагулянтной терапией; межлекарственные взаимодействия; возможности гастропротекции у пациентов, принимающих ПОАК. В реальной клинической практике причиной не назначения или необоснованного снижения дозы ПОАК является опасение кровотечений. При этом риски кровотечений, как правило, переоцениваются. Знание факторов риска кровотечений, прогностических шкал и управление факторами риска – подход, способный повысить безопасность антикоагулянтной терапии. В клинической практике выбор идеального ПОАК, кроме учета риска кровотечений, должен базироваться на комплексной оценке, включая возраст пациента, риск инсульта и коронарных событий, функцию почек, а также прогнозируемую комплаентность.

Ключевые слова: апиксабан; ривароксабан; дабигатран; фармакокинетика; биодоступность; нежелательные лекарственные реакции; желудочно-кишечные кровотечения.

Как цитировать:
Бакулина Н.В., Тихонов С.В., Апресян А.Г., Ильяшевич И.Г. Особенности применения пероральных антикоагулянтов в клинической практике: фокус на желудочно-кишечные осложнения // Cardiac Arrhythmias. 2023. Т. 3, № 2. С. 29–40. DOI: https://doi.org/10.17816/cardar321821

Рукопись получена: 20.05.2023 **Рукопись одобрена:** 12.06.2023 **Опубликована:** 31.07.2023

ЭКО•ВЕКТОР

Все права защищены
© Эко-Вектор, 2023

BACKGROUND

The hemostasis system is a complex biological system of adaptive reactions aimed at maintaining the liquid state of circulating blood, arrest of bleeding in the case of vessel damage, and lysing blood clots that have fulfilled their function. Hemostasis is implemented to balance the interaction between coagulation and anticoagulation systems. The coagulation system includes a vascular platelet and coagulation aspect, whereas the while anticoagulation system consists of natural anticoagulants and a fibrinolysis system that lyses blood clots [1, 2]. Under physiological conditions, a thrombus occurs at the site of vascular wall damage to stop bleeding and minimize the occurrence of massive blood loss. A thrombus represents a lifetime blood clot in a vessel lumen, which is a result of coagulation system activation [2].

Rudolf Virchow, a German scientist, conducted a series of studies in the mid-to-late XIX century and identified the main predisposing factors for thrombogenesis. According to the "Virchow triad", a blood clot is formed for three main reasons, namely, blood flow impairment (slowdown and turbulence), vessel wall damage, including endothelium pathology, and change in the blood component [3].

In the early stages of anthropogenesis, bleeding risks in placental mammals and anthropoid apes were extremely high. Evolutionary changes in the environment when anthroposociogenesis contributed to a decrease in the probability of traumatic injuries and bleeding in the presence of multiple risk factors for pathological thrombosis. Physical inactivity, eating disorders, and excessive accumulation of adipose tissue can cause the development of several diseases of the endocrine and cardiovascular systems, which increase thrombosis risk. Endothelial dysfunction and atherosclerotic plaques predispose individuals to arterial thrombosis formation. Insufficient physical activity and venous bed pathology increase the risk of deep vein thrombosis (DVT) of the lower extremities and thromboembolic complications. Diseases of civilization (obesity, arterial hypertension, dyslipidemia, and type 2 diabetes mellitus) are significant risk factors for both arterial and venous thromboses [4–7].

In the 21st century, diseases with a significant or main role of thrombogenesis in pathogenesis are a key medical problem. Myocardial infarctions and ischemic strokes are topical examples of arterial thrombosis. Lower-limb DVT, including those complicated by pulmonary artery thromboembolia (PATE), are common variants of venous thrombosis. In patients with atrial fibrillation (AF), the left atrial appendage is a common site for thrombus formation. From this area, a thrombus can migrate into the aorta and enter the internal carotid artery, causing acute ischemic cerebrovascular accident (ACVA) [3, 8].

Observational case-control cohort studies have contributed to the identification of risk factors for thrombosis, thromboembolic complications, and creation of scales that predict the risks of thrombotic complications, such as the Caprini scale (risk of thrombotic complications in patients undergoing surgery), CHA2DS2VASc scale (risk of thrombotic complications in patients with AF), Geneva index (risk of PATE), and Wells scale (risk of PATE). Physicians used these scales to assess the risk of thrombotic complications and the need for antithrombotic prevention [9–11]. Antiplatelet agents, anticoagulants, and fibrinolytic agents are drugs used in clinical practice for the treatment of thrombosis and thromboembolic complications. Antiplatelet agents are key drugs for the prevention and treatment of arterial thrombosis, myocardial infarction, and ACVA. Anticoagulants are used to prevent and treat arterial and venous thromboses [12]. A special group is represented by patients with ischemic ACVA who have the highest risk of thromboembolic complications. According to Diener's law, after exclusion on the day of a hemorrhagic stroke, the anticoagulant therapy is resumed according to the principle of 1:3:6:12. It is performed on day 1 in patients with a transient ischemic attack, day 3 with a minor stroke, day 6 with a moderate stroke, and day 12 with a severe stroke [13]. Patients with ACVA often have not only chronic diseases of the gastrointestinal tract (GIT) but also stress-dependent lesions of the gastroduodenal mucosa (Cushing's ulcer). The peculiarity of the management of these patients is the lack of practice of routine endoscopic examination of the upper GIT and the combined use of anticoagulants with proton pump inhibitors (PPIs), including parenteral forms [14–16].

Currently, direct oral anticoagulants (DOACs) are the main anticoagulant drugs used for prophylaxis in outpatients. These drugs are characterized by predictable pharmacokinetics and pharmacodynamics and a favorable efficacy and safety profile. Unlike heparin and low-molecular-weight heparins, DOACs have an oral route of administration and are not inferior in efficiency, and some of them are superior to the vitamin K antagonist warfarin [17].

In the Russian Federation, three drugs belonging to the DOAC class are registered, namely, dabigatran, a reversible competitive direct inhibitor of thrombin, and rivaroxaban and apixaban which are reversible, highly selective direct inhibitors of factor Xa [18–21].

In actual clinical practice, the fear of bleeding is a reason for not prescribing or unreasonably reducing the dose of DOACs. Moreover, bleeding risks are usually overestimated [22]. In AF, the HAS-BLED scale is recommended to assess the risk of hemorrhage during DOAC therapy [23]. According to current clinical guidelines, a high bleeding risk should not be a reason to refuse anticoagulant therapy because the benefits of treatment (reducing the risk of thrombosis) outweigh significantly bleeding risks in various locations [20].

The awareness of bleeding risk factors, prognostic scales, and management of risk factors can improve the safety of anticoagulant therapy. In clinical practice, the choice of the ideal DOAC, in addition to considering the bleeding risk,

should be based on a comprehensive assessment, including an assessment of the patient's age, stroke risk, coronary events, renal function, and predicted compliance.

Pharmacokinetics of direct oral anticoagulants

To date, a series of randomized double-blind international studies have demonstrated the efficiency of DOACs in preventing stroke and systemic embolic events in patients with non-valvular AF [24–27].

Literature data demonstrate that DOACs have predictable pharmacokinetics, fewer drug interactions, and better efficacy and safety profile than warfarin. The two classes of DOACs, direct thrombin inhibitors and direct factor Xa inhibitors, are fixed-dose targeted drugs, do not require international normalized ratio monitoring, and are characterized by a broad therapeutic index, rapid onset of action, and short half-life [27]. The standard doses of DOACs (dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and apixaban 5 mg twice daily) have been reported in patients with AF [17]. In some clinical situations, for example, in renal failure, drug doses may be revised in accordance with current instructions.

The safety of the use of these drugs in specific clinical situations and the prediction of risk of adverse drug reactions (ADRs), which are mainly dose-dependent and predictable, remains unestablished [28]. Moreover, the pharmacokinetic parameters of the main representatives of DOACs and their safety profiles differ significantly. These pharmacokinetic characteristics are presented in Table 1 [19–21].

Dabigatran is a prodrug metabolized by esterase enzymes. Genetic polymorphism of esterases can cause significant differences in drug metabolism and pharmacokinetics, acting as a factor that determines the risk of side effects, particularly bleeding [29]. Dabigatran has a high polarity that prevents absorption in the GIT. Food intake slows down significantly drug absorption but does not change bioavailability (6.5%). Considering low bioavailability, creation of high concentrations in the intestinal lumen, and partial activation of the drug by intestinal esterase, dabigatran etexilate can locally affect the intestinal mucosa, causing damage and bleeding, including from existing defects [30, 31]. After the oral administration, the drug reaches maximum concentrations in the blood after 0.5–2 h, and 85% is excreted by the kidneys; therefore, a creatinine clearance of < 30 mL/min is a contraindication to the prescription of dabigatran. To reduce the risk of ADR in patients aged > 80 years, patients with erosive esophagitis and gastritis, and other patients with a high bleeding risk, a reduced dose of dabigatran is recommended (110 mg two times a day). Given that the prodrug of dabigatran etexilate is a P-glycoprotein (P-gp) substrate, co-administration of dabigatran with inhibitors and inducers of the P-gp transporter has been studied. The simultaneous use of P-gp inhibitors (amiodarone, verapamil, quinidine, ketoconazole for systemic use, dronedarone, ticagrelor, and clarithromycin) led to an increase in the plasma concentrations of dabigatran. In a non-interventional prospective study of patients aged > 85 years, the bleeding risk increased approximately sixfold when dabigatran was co-administered with the potent P-gp inhibitor amiodarone [32]. In accordance with the instructions, the simultaneous use of dabigatran with ketoconazole, cyclosporine, itraconazole, tacrolimus, and dronedarone is contraindicated, and they must be cautiously used together with amiodarone, verapamil, quinidine, and ticagrelor. When combined with verapamil, the dose of dabigatran should be reduced to 110 mg twice daily [20].

Rivaroxaban is rapidly absorbed and reaches peak plasma concentrations within 2–4 h. Food intake increases bioavailability up to 100%, probably due to the solubilization and dissolution of the drug. Rivaroxaban is a substrate for P-gp and is metabolized in the liver, with the participation of the cytochrome P450 system (CYP3A4 and CYP2J2) [33].

Table 1. Main pharmacokinetic parameters of direct oral anticoagulants

Indicator	Rivaroxaban	Apixaban	Dabigatran
Mechanism of action – point of application	Xa inhibitor	Xa inhibitor	IIa inhibitor
Bioavailability, %	66–100*	~50	6.5
Prodrug	no	no	yes
T1/2, hours	5–13	12	12–14
T max, hours	2–4	3–4	0.5–2
Plasma protein binding, %	>90	87	35
Renal excretion, %	33	27	85
Hepatic metabolism	Moderate	Moderate	Low
Metabolism in CYP450	CYP3A4, CYP2J2	CYP3A4/5	No
Drug interactions	CYP3A4 inhibitors, P-glycoprotein	CYP3A4 inhibitors	Rifampicin, quinidine, amiodarone, P-glycoprotein inhibitors
Dosing regimen	Once daily	Twice a day	Twice a day

* The bioavailability of rivaroxaban is dose-dependent: for 10 mg, approximately 100% regardless of food intake; for 15 mg and 20 mg, approximately 66% when taken on an empty stomach and approximately 100% when taken with food.

The drug has a double route of excretion, which provides greater safety in patients with hepatic and/or renal insufficiency. Considering the direct excretion of nearly a third of the drug in the urine, creatinine clearance of 30–49 mL/min is an indication for prescribing a reduced dose of 15 mg once a day. The drug is contraindicated in patients with creatinine clearance of < 15 mL/min [19].

Apixaban is absorbed mainly in the small intestine, with a drug bioavailability of 50% [34]. Apixaban is metabolized by CYP3A4/5 and secondarily by sulfotransferase 1A1 and excreted in the urine (25%) and hepatobiliary route (75%). The drug should be used with caution in patients with severe renal insufficiency, and it is contraindicated in patients with a creatinine clearance of < 15 mL/min. A reduced dose of 2.5 mg twice daily is indicated if two or more of the factors are present: age ⩾ 80 years, body weight < 60 kg, and plasma creatinine of ⩾ 1.5 mg/dL (133 μmol/L). In addition, a dose of 2.5 mg twice a day is prescribed for patients with creatinine clearance of 15–29 mL/min [21]. A retrospective study by Hanigan et al. published in 2020 revealed that the co-administration of moderate CYP3A4 inhibitors (amiodarone, diltiazem, verapamil, erythromycin, etc.) with apixaban or rivaroxaban for at least 3 months was associated with a higher overall bleeding risk compared with DOAC monotherapy [35]. Clinically significant drug interactions of major DOACs are presented in Table 2.

All DOACs are contraindicated in patients with liver diseases accompanied by coagulopathy, significant bleeding risk, and Child–Pugh class C liver function impairment [19–21]. According to the European Heart Rhythm Association (EHRA) of 2021, rivaroxaban is contraindicated in patients with Child–Pugh grade B hepatic cirrhosis, whereas other DOACs can be used with caution. In the latest updates of the 2021 EHRA European Clinical Guidelines, unreasonable frequent prescriptions of reduced doses of DOACs received much interest. Experts emphasize the need for routine use of the studied standard doses of anticoagulants and reduced doses only in accordance with published and approved criteria. When choosing a dose, the interests of the patient, whose stroke risk prevails over the risk of hemorrhagic complications, must be considered [36]. Russian researchers take a similar position, pointing to an unreasonably frequent reduction in DOAC doses [37].

Effect of direct oral anticoagulants on the gastrointestinal mucosa

Despite the relatively favorable safety profile of DOACs, bleeding risk, including GI bleeding, is predominant and determines the choice of DOACs. Currently, no studies have directly compared the safety and efficacy of various DOACs. Randomized clinical trials have shown that the incidence of various hemorrhagic complications during anticoagulant therapy is 2–5% annually [38, 40]; however, when analyzing registries of patients with AF receiving long-term DOAC therapy, the frequency of major bleeding was approximately 0.5% [41, 42]. GI bleeding account for at least half of the total cases of major bleeding [43–45]. In a long-term prospective study within the REVAZA registry, the incidence of bleeding from the upper GIT was registered three times more often than that from the lower GIT [45].

Considering pharmacokinetics and pharmacodynamics, DOACs should not have a direct damaging effect on the GI mucosa. Mihalkanin et al. demonstrated that within 3 months of monitoring patients who initially had no lesions in the gastric mucosa and received DOACs, no clinically significant GI hemorrhage (GIH) was detected [46]. A high

Table 2. Clinically significant drug interactions between direct oral anticoagulants and commonly used drugs [19–21]

Agent	Apixaban	Dabigatran	Rivaroxaban
Antibacterial drugs			
Clarithromycin	No	No	No
Erythromycin	No	No	No
NSAIDs and antiplatelet agents			
NSAIDs	*	*	*
Aspirin	*	*	*
Clopidogrel	Yes	*	No
Ticagrelor	No	*	No
Antiarrhythmic drugs			
Amiodarone	Yes	*	No
Quinidine	Yes	Yes	No
Verapamil	No	*	No
Diltiazem	No	No	No

Note. Yes, there is an interaction (it is not advisable to prescribe); no, no clinically significant interaction (preferably prescribed); * with caution (subject to the measures specified in the instructions, taking into account possible changes in the concentration).

bleeding risk is associated with the "manifesting effect" of drugs on existing mucosal defects [47]. Thus, in a meta-analysis of 43 studies involving > 160,000 patients treated with DOACs, the incidence of GIH from the upper regions was 1.5% annually and 1.0% from the lower ones, which were mainly caused by tumors of various localization, diverticulitis, colon polyps, ulcerative colitis, hemorrhoids, and rectal fissures [48].

Thus, DOACs have a "manifesting" effect on the already altered GI mucosa, and bleeding risk during anticoagulant therapy depends on the profile of a patient and risk predictors. Epidemiological studies have shown that GIH risks are significantly increased in patients with comorbidities. The main predictors of bleeding were *Helicobacter pylori* infection with an odds ratio (OR) of 4.75; age > 75 years, OR of 4.52; alcohol addiction, OR of 2.5; renal failure, OR of 1.67; coronary heart disease, OR of 1.37; chronic heart failure, OR of 1.25; and glucocorticosteroid intake, OR of 1.17 [49, 50].

Before prescribing DOACs, in terms of preventing the risk of complications, erosive and ulcerative damage to the mucous membrane, *H. pylori* infection, oncopathology, diverticulitis, and other clinically important diseases of the GIT, which are potential sources of bleeding, must be ruled out. In this regard, prompt endoscopic examination of the upper and lower GIT is required [51]. To determine the approach of managing a patient receiving anticoagulant therapy, with GI bleeding, the classification of hemorrhagic complications based on the GARFIELD-AF registry (Table 3) is used [37].

Minor hemorrhagic bleeding or "vexatious" hemorrhage does not require medical intervention, changes in the treatment regimen, does not change the patient's habitual activity, and includes minor hemorrhoidal bleeding, minor nosebleeds, subcutaneous hematomas, and gingival bleeding. According to the ORBIT-AF registry, which included 7372 patients on DOAC therapy, 20% experienced "vexatious" bleeding, whereas 96% continued anticoagulant therapy without changes. Over the next 6 months, when comparing patients with "vexatious" bleeding and those without it, the risk of major hemorrhagic complications was not different. Thus, minor hemorrhagic complications are not prodromes of major bleeding, do not pose a serious threat to health, do not affect the long-term prognosis of patients, and do not serve as an indication for the discontinuation of therapy [52]. Kirchhof et al. demonstrated that when anticoagulant therapy is interrupted, the risk of stroke increases, namely, by 6.2% with temporary discontinuation and by 25.6% with long-term cancelation [53]. According to the Russian clinical guidelines of 2020, to prevent thromboembolic complications in patients with AF and minor "vexatious" bleeding, postponing the intake of one dose of DOAC until the bleeding stops is sufficient [51].

Currently, the scientific literature presents heterogeneous data on the comparative safety of the main DOACs in terms of the development of GIT complications, which is associated with different study designs.

According to the Italian National Pharmacovigilance Network, 7273 serious ADRs were registered in 959.231 patients treated with DOACs — 3342/294721 (1.13%) for dabigatran, 2032/317359 (0.64%) for rivaroxaban, and 1492/294721 (0.50%) for apixaban. The most frequent severe ADRs were GI bleeding (41.2% of cases) [54].

In a national population study, Ingason et al. analyzed the data of 8892 patients who received therapy with various DOACs between 2014 and 2019 (Table 4) [55].

Ingason et al. revealed that rivaroxaban therapy was associated with an increased overall risk of GIH and risk of major GIH compared with apixaban and dabigatran. The causes of the increased risk in patients taking rivaroxaban are unclear; however, the findings may be related to the study design.

Higher bleeding rates with rivaroxaban intake should be further analyzed. A randomized controlled trial of the efficacy and safety of rivaroxaban (ROCKET AF) involved more patients with severe diseases who initially had high bleeding risk [56].

GIH prevention

DOACs are used to prevent and treat potentially life-threatening conditions (thrombosis and PATE); however, their uses are at risk of ADRs, particularly bleeding. In clinical

Table 3. Classification of hemorrhagic complications based on the GARFIELD-AF registry

Major hemorrhagic complications	Overt bleeding with at least one of the following: • Decrease in hemoglobin by ≥2 g/dL or • Need for blood transfusion ≥2 doses of blood components • Clinically significant localization (intracranial, intraspinal, intraocular, cardiac tamponade, intra-articular, intramuscular with the development of compression syndrome, and retroperitoneal bleeding) • Fatal bleeding
Minor clinically significant hemorrhagic complications	Overt bleeding that did not meet the criteria for major hemorrhage but required medical treatment, a change in the treatment regimen by the doctor, or accompanied by pain, discomfort, or a change in the patient's usual activity
Minor hemorrhagic complications	All other bleeding events that do not meet the criteria for major and minor clinically significant hemorrhage

Table 4. Incidence of gastrointestinal (GI) hemorrhage (GIH) according to a population study (*n* = 8892)

Therapy DOACs	Events per 100 people/years
Total of GI hemorrhage	
Apixaban	2.4
Dabigatran	1.6
Rivaroxaban	3.2
Major GI hemorrhage	
Apixaban	1.4
Dabigatran	1.1
Rivaroxaban	2.0
Bleeding from the upper GI tract	
Apixaban	0.8
Dabigatran	0.4
Rivaroxaban	1.0
Bleeding from the lower GI tract	
Apixaban	1.3
Dabigatran	1.2
Rivaroxaban	1.6

practice, to assess the risk of all hemorrhagic complications when using DOACs, the HAS-BLED scale is recommended. Patients who scored ⩾ 3 points on this scale have a high bleeding risk [57]. According to the algorithm of the Eurasian Association of Therapists for the Prevention of Hemorrhagic Complications, patients with AF receiving DOACs should have normal blood pressure, minimized risk of drug interactions, and refused or minimized alcohol consumption, and the efficiency and safety of anticoagulant therapy must be evaluated at least once every 12 months, as well as liver and kidney function. Patients aged > 75 years should be followed up every 6 months, and those with creatinine clearance < 60 mL/min once every N months (N = creatinine clearance /10) [21, 58].

Before initiating DOAC therapy, erosive and ulcerative lesions of the GI mucosa must be ruled out. Patients with high bleeding risk require correction of modifiable risk factors, such as eradication of *H. pylori*, minimizing or canceling glucocorticosteroids and NSAIDs, and use safer NSAIDs and antiplatelet agents (highly selective cyclooxygenase-2 inhibitors and adenosine diphosphate receptor blockers), and acid-suppressive and gastroprotective therapy [51].

The COMPASS study was the first clinical randomized trial to evaluate the efficacy and safety of PPIs in patients receiving DOACs. That study revealed that PPIs did not affect the GIH risk when using DOACs; however, they had a positive effect on patients from the high-risk group [59]. Thus, PPIs are recommended for all patients who scored ⩾ 3 on the HAS-BLED scale [63]. PPIs should also be given to patients receiving dual or triple antithrombotic therapy, patients taking a combination of DOACs with NSAIDs and/or glucocorticosteroids, and patients with concomitant acid-related diseases [60].

In some clinical situations (hypo- or anacidity, duodenogastric reflux, microcirculation disorders, and use of NSAIDs and other drugs that affect adversely the GI mucosa), antacids, alginates, rebamipide, bismuth tripotassium dicitrate, and ursodeoxycholic acid can be used. No clinical studies have evaluated the efficiency of these drugs in patients receiving anticoagulants. Clinical studies have demonstrated the effectiveness of rebamipide in patients with NSAID gastroenteropathy by increasing the concentration of prostaglandins in the GI mucosa, increasing the synthesis of glycoproteins, and activating epidermal growth factor and its receptor expression [61–64].

CONCLUSIONS

Currently, DOACs have a wide range of clinical indications, including the prevention and treatment of thrombotic and thromboembolic complications. Hemorrhagic complications, particularly from the GI tract, is the most common ADRs associated with DOAC therapy. When deciding on DOAC therapy, in each case, bleeding risk, age, risk of stroke or coronary events, renal function, and predicted adherence to the therapy prescribed must be considered. To minimize GIH risk, risk factors for bleeding must be identified, modifiable factors altered, potential drug interactions monitored, and, if necessary, acid-suppressive and gastroprotective therapy prescribed.

ADDITIONAL INFORMATION

Competing interests. The authors declare that they have no competing interests.

Funding source. This study was not supported by any external sources of funding.

REFERENCES

1. Pathophysiology: textbook: Ed. by V.V. Novitsky, E.D. Goldberg, O.I. Urazova. Moscow: GEOTAR-Media, 2009. Vol. 2. 640 p. (In Russ.)
2. Forge BI. Cellular and molecular mechanisms of regulation of the hemostasis system in normal and pathology. Chita: Express Publishing, 2010. (In Russ.)
3. Watson T, Shantsila E, Lip GY. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet.* 2009;373(9658): 155–166. DOI: 10.1016/S0140-6736(09)60040-4
4. Lijfering WM, Rosendaal FR, Cannegieter SC. Risk factors for venous thrombosis — current understanding from an epidemiological point of view. *Br J Haematol.* 2010;149(6):824–833. DOI: 10.1111/j.1365-2141.2010.08206.x
5. Sloan E, Wright T, Zuo Y. Identifying additional risk factors for arterial and venous thrombosis among pediatric antiphospholipid antibodies carriers. *Lupus*. 2021;30(5):828–832. DOI: org/10.1177/09612033211002256
6. Samad F, Ruf W. Inflammation, obesity, and thrombosis. *Blood*. 2013;122(20):3415–3422. DOI: org/10.1182/blood-2013-05-427708
7. Previtali E, Bucciarelli P, Passamonti SM, et al. Risk factors for venous and arterial thrombosis. *Blood Transfus*. 2011;9(2):120–138
8. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics — 2010 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2019;121;e46–e215. DOI: 10.1161/CIRCULATIONAHA.109.192667
9. Bergmark BA, Bhatt DL, Braunwald E, et al. Risk Assessment in Patients With Diabetes With the TIMI Risk Score for Atherothrombotic Disease. *Diabetes Care*. 2018;41(3):577–585. DOI: org/10.2337/dc17-1736
10. Cetinkal G, Kocas BB, Ser OS, et al. Assessment of the Modified CHA2DS2VASc Risk Score in Predicting Mortality in Patients Hospitalized With COVID-19. *Am J Cardiol*. 2020;135:143–149. DOI: org/10.1016/j.amjcard.2020.08.040
11. Tamizifar B, Fereyduni F, Esfahani MA, et al. Comparing three clinical prediction rules for primarily predicting the 30-day mortality of patients with pulmonary embolism: The "Simplified Revised Geneva Score," the "Original PESI," and the "Simplified PESI". Adv Biomed Res. 2016;5:137. DOI: org/10.4103/2277-9175.187372
12. Clinical Pharmacology: Study / Ed. by V.G. Kukesa. Moscow: GEOTAR-Media, 2006. 944 p. (In Russ.)
13. Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace*. 2015;17:1467–1507. DOI: org/10.1093/europace/euv309
14. Erosive-ulcerative lesions of the gastroduodenal zone in stressful situations (operations, injury and shock) and severe diseases of internal organs. *KRSU Bulletin*. 2014;14(1):179–182. (In Russ.)
15. Tavlueva EV, Savkova ON, Zernova EV et al. Frequency of use of oral anticoagulants in real-life clinical practice in patients hospitalized with acute ischemic stroke. *Russian Journal of Cardiology*. 2022;12(27):74–79. (In Russ.)
16. Moiseev S. Direct oral anticoagulants for prevention of recurrent stroke in patients with atrial fibrillation. *Clin Pharmacologiya i terapiya*. 2021;30(3):57–66. (In Russ.) DOI: 10.32756/0869-5490-2021- 3-57-66
17. Raval AN, Cigarroa JE, Chung MK, et al. Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association. *Circulation*. 2017;135(10):e647. DOI: 10.1161/CIR.0000000000000477
18. Clinical guidelines: Atrial fibrillation and flutter. Ministry of Health of the Russian Federation. Moscow, 2020. 185 p. (In Russ.)
19. Official Instruction for the drug Xarelto®. https://www.rlsnet.ru/tn_index_id_43277.htm [Available from: 23.07.2021]. (In Russ,)
20. Official Instructions for the drug Pradaxa®. https://www.rlsnet.ru/tn_index_id_42850.htm [Available from: 23.07.2021]. (In Russ.)
21. Official Instruction for the drug Eliquis®. https://www.vidal.ru/drugs/eliquis__38823 [Available from: 23.07.2021]. (In Russ.)
22. Camm AJ, Amarenco P, Haas S, et al. XANTUS: rationale and design of a noninterventional study of rivaroxaban for the prevention of stroke in patients with atrial fibrillation. *Vasc Health Risk Manag*. 2014;10:425–434. DOI: 10.2147/VHRM.S63298
23. Lip G, Windecker S, Huber K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions. *European Journal of Cardiology*. 2014;35(45): 3155–3179. DOI: 10.1093/eurheartj/ehu298
24. Hindricks G, Potpara T, Dagres N, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42(5): 373–498. DOI: 10.1093/eurheartj/ehaa612.
25. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139–1151. DOI: 10.1056/NEJMoa0905561
26. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992. DOI: 10.1056/NEJMoa1107039.
27. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–2104. DOI: 10.1056/NEJMoa1310907
28. Karcioglu O, Zengin S, Ozkaya B, et. al. Direct (New) Oral Anticoagulants (DOACs): Drawbacks, Bleeding and Reversal. *Cardiovasc Hematol Agents Med Chem*. 2022;20(2):103-113. DOI: 10.2174/1871525719666210914110750. PMID: 34521332.
29. Pare G, Eriksson N. Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation.* 2013;127;1404–1412. DOI: org/10.1161/CIRCULATIONAHA.112.001233
30. Blech S, Ebner T, Ludwig-Schwellinger E, et al. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. *Drug Metab Dispos.* 2008;36:386–399. PMID: 18006647. DOI: 10.1124/dmd.107.019083
31. Laizure SC, Parker RB, Herring VL, et al. Identification of carboxylesterase-dependent dabigatran etexilate hydrolysis. *Drug Metab Dispos*. 2014;42(2):201–206. DOI: 10.1124/dmd.113.054353. Epub 2013 Nov 8. PMID: 24212379

32. Bernier M, Lancrerot SL, Parassol N, et al. Therapeutic Drug Monitoring of Direct Oral Anticoagulants May Increase Their Benefit-Risk Ratio. *J Cardiovasc Pharmacol*. 2020;76(4):472–477. DOI: 10.1097/FJC.0000000000000870

33. Kreutz R. Pharmacokinetics and pharmacodynamics of rivaroxaban--an oral, direct factor Xa inhibitor. *Curr Clin Pharmacol*. 2014;9(1):75–83. DOI: 10.2174/15748847086661311111204658

34. Frost C, Garonzik S, Shenker A, et al. Apixaban Single-Dose Pharmacokinetics, Bioavailability, Renal Clearance, and Pharmacodynamics Following Intravenous and Oral Administration. *Clin Pharmacol Drug Dev*. 2021;10(9):974–984. DOI: 10.1002/cpdd.990

35. Hanigan S, Das J, Pogue K, et al. The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding. *J Thromb Thrombolysis*. 2020;49(4): 636–643. DOI: 10.1007/s11239-020-02037-3. PMID: 31925665

36. Steffel J, Collins R, Antz M. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. *Europace*. 2021:1–65. DOI:10.1093/europace/euab065

37. Ionin VA, Bliznyuk OI, Baranova EI, et al. Anticoagulant therapy in patients with non-valvular atrial fibrillation in real clinical practice: unreasonable use of reduced doses. *Rational Pharmacotherapy in Cardiology*. 2021;2(17):206–211. DOI: 10.20996/1819-6446-2021-03-04

38. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(15):955–96. DOI: 10.1016/S0140-6736(13)62343-62350

39. Beyer-Westendorf J, Förster K, Pannach S, et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. *Blood*. 2014;124(6):955–62. DOI: 10.1182/blood-2014-03-563577.124:955-962

40. Testa S, Ageno W, Antonucci E, et al. Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry. *InternEmergMed*. 2018;13(7):1051–1058. DOI: 10.1007/s11739-018-1877-z

41. Cangemi DJ, Krill T, Weideman R ed al. A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin. *Am J Gastroenterol*. 2017;112(5):734–739. DOI: 10.1038/ajg.2017.39.

42. Kakkar AK, Mueller I, Bassand JP, et al «International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD)». *AHJ*. 2012;163(1):13–19. DOI: 10.1016/j.ahj.2011.09.011

43. Becattini C, Franco L, Beyer-Westendorf J, et al. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life. *Int J Cardiol*. 2017;227:261–266. DOI: 10.1016/j.ijcard.2016.11.117

44. Yuhara H, Corley DA, Nakahara F, et al. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis. *J Gastroenterol*. 2014;49:992–1000. DOI: 10.1007/s00535-013-0905-z

45. Kropacheva ES, Khakimova MB, Krivosheeva EN, et al. Severe gastrointestinal bleeding in patients with atrial fibrillation receiving oral anticoagulants (based on REGistry of long-term AnTithrombotic TherApy – REGATTA). *Terapevticheskii Arkhiv (Ter. Arkh.)*. 2021;93 (9):1037–1043. DOI: 10.26442/00403660.2021.09.201019

46. Mihalkanin L, Stancak B. The Impact of Novel Anticoagulants on the Upper Gastrointestinal Tract Mucosa. *Medicina (Kaunas)*. 2020;56(7):363. DOI: 10.3390/medicina56070363.

47. Camm AJ, Pinto FJ, Hankey GJ, et al. Writing Committee of the Action for Stroke Prevention alliance. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation. *Europace*. 2015;17(7):1007-1017. DOI: 10.1093/europace/euv068. PMID: 26116685

48. Miller CS, Dorreen A, Martel M; et al. Risk of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15(11):1674–1683.e3. DOI:10.1016/j.cgh.2017.04.031

49. Kirchhof P, Radaideh G, Kim YH, et al. Global XANTUS program Investigators. Global Prospective Safety Analysis of Rivaroxaban. *J Am Coll Cardiol*. 2018;7(2):141–153. DOI: 10.1016/j.jacc.2018.04.058

50. Lauffenburger JC, Farley JF, Gehi AK, et al. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. *Am J Cardiol*. 2015;115(8):1095–1101. DOI: 10.1016/j.amjcard.2015.01.539

51. Golitsyn SP, Panchenko EP, Kropacheva ES. Eurasian clinical guidelines for the diagnosis and treatment of atrial fibrillation. 2020. 95 p. (In Russ.)

52. O'Brien EC, Holmes DN, Thomas L, et al. Prognostic Significance of Nuisance Bleeding in Anticoagulated Patients With Atrial Fibrillation. *Circulation*. 2018;138(9):889–897.

53. Kirchhof P, Camm AJ, Goette A ed al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *N Engl J Med*. 2020;383(14):1305–1316. DOI: 10.1056/NEJMoa2019422

54. Lavalle C, Di Lullo L, Bellasi A, et al. Adverse Drug Reactions during Real-Life Use of Direct Oral Anticoagulants in Italy: An Update Based on Data from the Italian National Pharmacovigilance Network. *Cardiorenal Med*. 2020;10(4):266-276. DOI: 10.1159/000507046

55. Ingason AB, Hreinsson JP, Agustsson AS, et al. Warfarin is associated with higher rates of upper but not lower gastrointestinal bleeding compared to direct oral anticoagulants: a population-based propensity-weighted cohort study. *Clin. Gastroenterology Hepatol*. 2023;21(2):347-357. DOI: 10.1016/j.cgh.2022.06.033

56. Bansilal S, Bloomgarden Z, Halperin JL, et al. ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial). *Am Heart J*. 2015;170(4):675–682.e8. DOI: 10.1016/j.ahj.2015.07.006

57. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123(21):2363–2372. DOI: 10.1161/CIRCULATIONAHA.110.004747

58. Arutyunov GP, Fomin IV, Tarlovskaya EI, et al. Algorithm for assessing and modifying risk factors for minor bleeding in patients with atrial fibrillation receiving POAC therapy. Resolution of the Eurasian Association of Therapists. 2020. 30 p. (In Russ.)

59. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, Design and Baseline Characteristics of Participants in the

Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial. *Can J Cardiol*. 2017;33(8):1027–35. DOI: 10.1016/j.cjca.2017.06.001

60. Gralnek IM, Stanley AJ, Morris AJ, et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021. *Endoscopy*. 2021;53(3):300–332. DOI: 10.1055/a-1369-5274

61. Ishiyama H, Yamasaki K, Kanbe T. Effect of proamipide (OPC-12759) on gastric mucus secretion in rats. *Jpn Pharmacol Ther*. 1988;16:4103–109.

62. Yoshikawa T, Naito Y, Nakamura S, et al. Effect of rebamipide on lipid peroxidation and gastric mucosal injury induced by indometacin in rats. *Arzneimittelforschung*. 1993;43(12):1327–1330.

63. Suzuki M, Miura S, Mori M, et al. Rebamipide, a novel antiulcer agent, attenuates Helicobacter pylori induced gastric mucosal cell injury associated with neutrophil derived oxidant. *Gut*. 1994;35(10):1375–1378. DOI: 10.1136/gut.35.10.1375

64. Aihara M, Azuma A, Takizawa H, et al. Molecular analysis of suppression of interleukin-8 production by rebamipide in Helicobacter pylori-stimulated gastric cancer cell lines. 1998;43(9 Suppl): 174S–180S.

СПИСОК ЛИТЕРАТУРЫ

1. Патофизиология: учебник: в 2 т. / под ред. В.В. Новицкого, Е.Д. Гольдберга, О.И. Уразовой. Москва: ГЭОТАР-Медиа, 2009. Т. 2. 640 с.

2. Кузник Б.И. Клеточные и молекулярные механизмы регуляции системы гемостаза в норме и патологии. Чита: Экспресс-издательство, 2010.

3. Watson T., Shantsila E., Lip G.Y. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited // Lancet. 2009. Vol. 373, No. 9658. P. 155–166. DOI: 10.1016/S0140-6736(09)60040-4.

4. Lijfering W.M., Rosendaal F.R., Cannegieter S.C. Risk factors for venous thrombosis — current understanding from an epidemiological point of view // Br J Haematol. 2010. No. 6. P. 824–833. DOI: 10.1111/j.1365-2141.2010.08206.x

5. Sloan E., Wright T., Zuo Y. Identifying additional risk factors for arterial and venous thrombosis among pediatric antiphospholipid antibodies carriers // Lupus. 2021. Vol. 30, No. 5. P. 828–832. DOI: 10.1177/09612033211002256

6. Samad F., Ruf W. Inflammation, obesity, and thrombosis // Blood. 2013. Vol. 122, No. 20. P. 3415–3422. DOI: 10.1182/blood-2013-05-427708

7. Previtali E., Bucciarelli P., Passamonti S.M., et al. Risk factors for venous and arterial thrombosis // Blood Transfus. 2011. Vol. 9, No. 2. P. 120–138.

8. Lloyd-Jones D., Adams R.J., Brown T.M. et al. Heart disease and stroke statistics - 2010 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee // Circulation. 2019. Vol. 121. P. e46–e215. DOI: 10.1161/CIRCULATIONAHA.109.192667

9. Bergmark B.A., Bhatt D.L., Braunwald E., et al. Risk Assessment in Patients With Diabetes With the TIMI Risk Score for Atherothrombotic Disease // Diabetes Care. 2018. Vol. 41, No. 3. P. 577–585. DOI: 10.2337/dc17-1736

10. Cetinkal G., Kocas B.B., Ser O.S., et al. Assessment of the Modified CHA2DS2VASc Risk Score in Predicting Mortality in Patients Hospitalized With COVID-19 // Am J Cardiol. 2020. Vol. 135. P. 143–149. DOI: org/10.1016/j.amjcard.2020.08.040

11. Tamizifar B., Fereyduni F., Esfahani M.A., et al. Comparing three clinical prediction rules for primarily predicting the 30-day mortality of patients with pulmonary embolism: The "Simplified Revised Geneva Score," the "Original PESI," and the "Simplified PESI" // Adv Biomed Res. 2016. Vol. 5. P. 137. DOI: org/10.4103/2277-9175.187372

12. Клиническая фармакология: учеб. / под ред. В.Г. Кукеса. М.: ГЭОТАР-Медиа, 2006. 944 с.

13. Heidbuchel H., Verhamme P., Alings M., et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015. Vol. 17. P. 1467–1507. DOI: 10.1093/europace/euv309

14. Батырова А.Н., Бердалина Г.С., Тажиева А.Е. и др. Эрозивно-язвенные поражения гастродуоденальной зоны при стрессовых ситуациях (операциях, травме и шоке) и тяжелых заболеваниях внутренних органов // Вестник КРСУ. 2014. Т. 14, № 1. С. 179–182.

15. Тавлуева Е.В., Савкова О.Н., Зернова Е.В. и др. Частота использования пероральных антикоагулянтов в реальной клинической практике у пациентов, госпитализированных с острым ишемическим инсультом // Российский кардиологический журнал. 2022. Т 12, № 27. С. 74–79.

16. Моисеев С.В. Прямые оральные антикоагулянты в профилактике повторного инсульта у пациентов с фибрилляцией предсердий // Клиническая фармакология и терапия. 2021. Т. 3, № 30. С. 57–66. DOI: 10.32756/0869-5490-2021- 3-57-66.

17. Raval A.N., Cigarroa J.E., Chung M.K., et al. Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting: A Scientific Statement From the American Heart Association // Circulation. 2017. Vol. 135, No. 10. P. e647. DOI: 10.1161/CIR.0000000000000477

18. Клинические рекомендации: Фибрилляция и трепетание предсердий. Москва, 2020. 185 с. https://scardio.ru/content/Guidelines/2020/Clinic_rekom_FP_TP-unlocked.pdf

19. Официальная инструкция к препарату Ксарелто®. https://www.rlsnet.ru/tn_index_id_43277.htm [дата обращения: 23.07.2021]

20. Официальная инструкция к препарату Прадакса®. https://www.rlsnet.ru/tn_index_id_42850.htm [дата обращения: 23.07.2021].

21. Официальная инструкция к препарату Эликвис®. https://www.vidal.ru/drugs/eliquis__38823 [дата обращения: 23.07.2021]

22. Camm A.J., Amarenco P., Haas S., et. al. XANTUS: rationale and design of a noninterventional study of rivaroxaban for the prevention of stroke in patients with atrial fibrillation // Vasc Health Risk Manag. 2014. Vol. 10: P.425–434. DOI: 10.2147/VHRM.S63298
23. Lip G., Windecker S., Huber K., et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions // Eur J of Cardiol. 2014. Vol. 35, No. 45. P. 3155–3179. DOI: 10.1093/eurheartj/ehu298
24. Hindricks G., Potpara T., Dagres N., et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC // Eur Heart J. 2021. Vol. 42, No. 5. P. 373–498. DOI: 10.1093/eurheartj/ehaa612
25. Connolly S.J., Ezekowitz M.D., Yusuf S., et al. Dabigatran versus warfarin in patients with atrial fibrillation // N Engl J Med. 2009. Vol. 361, No. 12. P. 1139–1151. DOI: 10.1056/NEJMoa0905561
26. Granger C.B., Alexander J.H., McMurray J.J., et al. Apixaban versus warfarin in patients with atrial fibrillation // N Engl J Med. 2011. Vol. 365. P. 981–992. DOI: 10.1056/NEJMoa1107039
27. Giugliano R.P., Ruff C.T., Braunwald E., et al. Edoxaban versus warfarin in patients with atrial fibrillation // N Engl J Med. 2013. Vol. 369. P. 2093–2104. DOI: 10.1056/NEJMoa1310907
28. Karcioglu O., Zengin S., Ozkaya B., et al. Direct (New) Oral Anticoagulants (DOACs): Drawbacks, Bleeding and Reversal // Cardiovasc Hematol Agents Med Chem. 2022. Vol. 20, No. 2. P. 103-113. DOI: 10.2174/1871525719666210914110750. PMID: 34521332
29. Pare G., Eriksson N. Genetic determinants of dabigatran plasma levels and their relation to bleeding // Circulation. 2013. Vol. 127. P. 1404–1412
30. Blech S., Ebner T., Ludwig-Schwellinger E., et al. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans // Drug Metab Dispos. 2008. Vol. 36. P. 386–399. DOI: 10.1124/dmd.107.019083
31. Laizure S.C., Parker R.B., Herring V.L., et al. Identification of carboxylesterase-dependent dabigatran etexilate hydrolysis // Drug Metab Dispos. 2014. Vol. 42, No. 2. P. 201–206. DOI: 10.1124/dmd.113.054353. Epub 2013 Nov 8. PMID: 24212379
32. Bernier M., Lancrerot S.L., Parassol N., et al. Therapeutic Drug Monitoring of Direct Oral Anticoagulants May Increase Their Benefit-Risk Ratio // J Cardiovasc Pharmacol. 2020. Vol. 76, No. 4. P. 472–477. DOI: 10.1097/FJC.0000000000000870
33. Kreutz R. Pharmacokinetics and pharmacodynamics of rivaroxaban--an oral, direct factor Xa inhibitor // Curr Clin Pharmacol. 2014. Vol. 9, No. 1. P. 75–83. DOI: 10.2174/15748847086661311112046 58
34. Frost C., Garonzik S., Shenker A., et al. Apixaban Single-Dose Pharmacokinetics, Bioavailability, Renal Clearance, and Pharmacodynamics Following Intravenous and Oral Administration // Clin Pharmacol Drug Dev. 2021. Vol. 10, No. 9. P. 974–984. DOI: 10.1002/cpdd.990
35. Hanigan S., Das J., Pogue K., et al. The real world use of combined P-glycoprotein and moderate CYP3A4 inhibitors with rivaroxaban or apixaban increases bleeding // J Thromb Thrombolysis. 2020. Vol. 49, No. 4. P. 636–643. DOI: 10.1007/s11239-020-02037-3
36. Steffel J., Collins R., AntzM. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation // Europace. 2021. P. 1–65. DOI: 10.1093/europace/euab065
37. Ионин В.А., Близнюк О.И., Баранова Е.И. и др. Антикоагулянтная терапия у больных с неклапанной фибрилляцией предсердий в реальной клинической практике: необоснованное применение сниженных доз // Рациональная Фармакотерапия в Кардиологии. 2021. Т. 2. № 17. P. 206–211. DOI: 10.20996/1819-6446-2021-03-04
38. Ruff C.T., Giugliano R.P., Braunwald E., et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials // Lancet. 2014. Vol. 383, No. 15. P. 955–96. DOI: 10.1016/S0140-6736(13)62343-62350
39. Beyer-Westendorf J., Förster K., Pannach S., et al. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry // Blood. 2014. Vol. 124, No. 6. P. 955-62. DOI: 10.1182/blood-2014-03-563577.124:955-962
40. Testa S., Ageno W., Antonucci E., et al. Management of major bleeding and outcomes in patients treated with direct oral anticoagulants: results from the START-Event registry // InternEmergMed. 2018. Vol. 13, No. 7. P.1051-1058. DOI: 10.1007/s11739-018-1877-z
41. Cangemi D.J., Krill T., Weideman R., ed al. A Comparison of the Rate of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral Anticoagulants or Warfarin // Am J Gastroenterol. 2017. Vol. 112, No. 5. P. 734-739. DOI: 10.1038/ajg.2017.39
42. Kakkar A.K., Mueller I., Bassand J.P., et al. «International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD) // AHJ. 2012. Vol. 163, No. 1. P. 13–19. DOI: 10.1016/j.ahj.2011.09.011
43. Becattini C., Franco L., Beyer-Westendorf J., et al. Major bleeding with vitamin K antagonists or direct oral anticoagulants in real-life // Int J Cardiol. 2017. Vol. 227. P. 261–6. DOI: 10.1016/j.ijcard.2016.11.117
44. Yuhara H., Corley D.A., Nakahara F., et al. Aspirin and non-aspirin NSAIDs increase risk of colonic diverticular bleeding: a systematic review and meta-analysis // J Gastroenterol. 2014. Vol. 49. P. 992–1000. DOI: 10.1007/s00535-013-0905-z
45. Кропачева Е.С., Хакимова М.Б., Кривошеева Е.Н. и др. Тяжелые желудочно-кишечные кровотечения у больных с фибрилляцией предсердий, получающих пероральные антикоагулянты (по данным двадцатилетнего наблюдения в рамках РЕГистра длительной Антитромботической ТерАпии – РЕГАТА) // Терапевтический архив. 2021. Т. 93, № 9. С. 1037–1043. DOI: 10.26442/00403660.2021.09.201019
46. Mihalkanin L., Stancak B. The Impact of Novel Anticoagulants on the Upper Gastrointestinal Tract Mucosa // Medicina (Kaunas). 2020. Vol. 56, No. 7. P. 363. DOI: 10.3390/medicina56070363.
47. Camm A.J., Pinto F.J., Hankey G.J., et al. Writing Committee of the Action for Stroke Prevention alliance. Non-vitamin K antagonist oral anticoagulants and atrial fibrillation guidelines in practice: barriers to and strategies for optimal implementation // Europace. 2015. Vol. 17, No. 7. P. 1007–1017. DOI: 10.1093/europace/euv068
48. Miller C.S., Dorreen A., Martel M., et al. Risk of Gastrointestinal Bleeding in Patients Taking Non-Vitamin K Antagonist Oral

Anticoagulants: A Systematic Review and Meta-analysis // Clin Gastroenterol Hepatol. 2017. Vol. 15, No. 11. P. 1674–1683.e3. DOI: 10.1016/j.cgh.2017.04.031

49. Kirchhof P., Radaideh G., Kim Y.H., et al. Global XANTUS program Investigators. Global Prospective Safety Analysis of Rivaroxaban // J Am Coll Cardiol. 2018. Vol. 72, No. 2. P. 141–153. DOI: 10.1016/j.jacc.2018.04.058

50. Lauffenburger J.C., Farley J.F., Gehi A.K., et al. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States // Am J Cardiol. 2015. Vol. 115, No. 8. P.1095–1101. DOI: 10.1016/j.amjcard.2015.01.539

51. Голицын С.П., Панченко Е.П., Кропачева Е.С. Евразийские клинические рекомендации по диагностике и лечению фибрилляции предсердий. 2020. 95 с.

52. O'Brien E.C., Holmes D.N., Thomas L., et al. Prognostic Significance of Nuisance Bleeding in Anticoagulated Patients With Atrial Fibrillation // Circulation. 2018. Vol. 138, No. 9. P. 889–897.

53. Kirchhof P., Camm A.J., Goette A., et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation // N Engl J Med. 2020. Vol. 383, No. 14. P. 1305–1316. DOI: 10.1056/NEJMoa2019422

54. Lavalle C., Di Lullo L., Bellasi A., et al. Adverse Drug Reactions during Real-Life Use of Direct Oral Anticoagulants in Italy: An Update Based on Data from the Italian National Pharmacovigilance Network // Cardiorenal Med. 2020. Vol. 10, No. 4. P. 266–276. DOI: 10.1159/000507046

55. Ingason A.B., Hreinsson J.P., Agustsson A.S., et al. Warfarin is associated with higher rates of upper but not lower gastrointestinal bleeding compared to direct oral anticoagulants: a population-based propensity-weighted cohort study // Clin. Gastroenterology Hepatol. 2023. Vol. 21. No. 2. P. 347–357. DOI: 10.1016/j.cgh.2022.06.033

56. Bansilal S., Bloomgarden Z., Halperin J.L., et al. ROCKET AF Steering Committee and Investigators. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF Trial // Am Heart J. 2015. Vol. 170, No. 4. P. 675–682.e8. DOI: 10.1016/j.ahj.2015.07.006

57. Eikelboom J.W., Wallentin L., Connolly S.J., et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial // Circulation. 2011. Vol. 123, No. 21. P. 2363–2372. DOI:10.1161/CIRCULATIONAHA.110.004747

58. Арутюнов Г.П., Фомин И.В., Тарловская Е.И. и др. Алгоритм оценки и модификации факторов риска небольших кровотечений у пациентов с фибрилляцией предсердий, получающих терапию ПОАК. Резолюция Евразийской ассоциации терапевтов. 2020. 30 с.

59. Bosch J., Eikelboom J.W., Connolly S.J., et al. Rationale, Design and Baseline Characteristics of Participants in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Trial // Can J Cardiol. 2017. Vol. 33, No. 8. P. 1027–1035. DOI: 10.1016/j.cjca.2017.06.001

60. Gralnek I.M., Stanley A.J., Morris A.J., et al. Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021 // Endoscopy. 2021. Vol. 53, No. 3. P. 300–332. DOI: 10.1055/a-1369-5274

61. Ishiyama H., Yamasaki K., Kanbe T. Effect of proamipide (OPC-12759) on gastric mucus secretion in rats // Jpn Pharmacol Ther. 1988. Vol. 16. P. 4103–109.

62. Yoshikawa T., Naito Y., Nakamura S., et al. Effect of rebamipide on lipid peroxidation and gastric mucosal injury induced by indometacin in rats // Arzneimittelforschung. 1993. Vol. 43, No. 12. P. 1327–1330.

63. Suzuki M., Miura S., Mori M., et al. Rebamipide, a novel antiulcer agent, attenuates Helicobacter pylori induced gastric mucosal cell injury associated with neutrophil derived oxidants // Gut. 1994. Vol. 35, No. 10. P. 1375–1378. DOI: 10.1136/gut.35.10.1375

64. Aihara M., Azuma A., Takizawa H., et al. Molecular analysis of suppression of interleukin-8 production by rebamipide in Helicobacter pylori-stimulated gastric cancer cell lines. 1998. Vol. 43, No. 9. P. 174S–180S.

AUTHORS INFO

Natalya V. Bakulina, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-4075-4096;
eLibrary SPIN: 9503-8950; e-mail: natalya.bakulina@szgmu.ru

***Sergey V. Tikhonov,** MD, Cand. Sci. (Med.), Assistant Professor;
ORCID: https://orcid.org/0000-0001-5720-3528;
eLibrary SPIN: 6921-5511; e-mail: sergeyvt2702@gmail.com

Anna G. Apresyan, MD, Cand. Sci. (Med.), Assistant Professor;
ORCID: https://orcid.org/0000-0003-0637-9384;
eLibrary SPIN: 8654-7705; e-mail: anna.apresyan@szgmu.ru

Inna G. Ilyashevich, MD, Cand. Sci. (Med.), Assistant Professor;
ORCID: https://orcid.org/0000-0002-5784-2634;
eLibrary SPIN: 3212-7518; e-mail: Inna.Ilyashevich@szgmu.ru

ОБ АВТОРАХ

Наталья Валерьевна Бакулина, д-р. мед.наук;
ORCID: https://orcid.org/0000-0003-4075-4096;
eLibrary SPIN: 9503-8950; e-mail: natalya.bakulina@szgmu.ru

***Сергей Викторович Тихонов,** канд. мед. наук, доцент;
ORCID: https://orcid.org/0000-0001-5720-3528;
eLibrary SPIN: 6921-5511; e-mail: sergeyvt2702@gmail.com

Анна Григорьевна Апресян, канд. мед. наук, доцент;
ORCID: https://orcid.org/0000-0003-0637-9384;
eLibrary SPIN: 8654-7705; e-mail: anna.apresyan@szgmu.ru

Инна Геннадьевна Ильяшевич, канд. мед. наук, доцент;
ORCID: https://orcid.org/0000-0002-5784-2634;
eLibrary SPIN: 3212-7518; e-mail: Inna.Ilyashevich@szgmu.ru

* Corresponding author / Автор, ответственный за переписку