Review article

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

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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.

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

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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 гастропroteкции 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:
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 fibrinolytic 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 typical examples of arterial thrombosis. Lower-limb DVT, including those complicated by pulmonary artery thromboembolism (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, 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].
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>
<thead>
<tr>
<th>Table 1. Main pharmacokinetic parameters of direct oral anticoagulants</th>
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<tr>
<td><strong>Indicator</strong></td>
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<tr>
<td><strong>Mechanism of action – point of application</strong></td>
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<tr>
<td><strong>Bioavailability, %</strong></td>
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<tr>
<td><strong>Prodrug</strong></td>
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<tr>
<td><strong>T1/2, hours</strong></td>
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<td><strong>T max, hours</strong></td>
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<tr>
<td><strong>Plasma protein binding, %</strong></td>
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<tr>
<td><strong>Renal excretion, %</strong></td>
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<tr>
<td><strong>Drug interactions</strong></td>
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<td><strong>Dosing regimen</strong></td>
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</table>

*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>
<thead>
<tr>
<th>Agent</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tbody>
<tr>
<td>Antibacterial drugs</td>
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</tr>
<tr>
<td>Clarithromycin</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>NSAIDs and antiplatelet agents</td>
<td></td>
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</tr>
<tr>
<td>NSAIDs</td>
<td>*</td>
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<tr>
<td>Aspirin</td>
<td>*</td>
<td>*</td>
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<tr>
<td>Clopidogrel</td>
<td>Yes</td>
<td>*</td>
<td>No</td>
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<tr>
<td>Ticagrelor</td>
<td>No</td>
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<td>No</td>
</tr>
<tr>
<td>Antiarrhythmic drugs</td>
<td></td>
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</tr>
<tr>
<td>Amiodarone</td>
<td>Yes</td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Verapamil</td>
<td>No</td>
<td>*</td>
<td>No</td>
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<td>Diltiazem</td>
<td>No</td>
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<td>No</td>
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</tbody>
</table>

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 GI 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**

<table>
<thead>
<tr>
<th>Major hemorrhagic complications</th>
<th>Overt bleeding with at least one of the following:</th>
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<tr>
<td></td>
<td>• Decrease in hemoglobin by ≥2 g/dL or</td>
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<td></td>
<td>• Need for blood transfusion ≥2 doses of blood components</td>
</tr>
<tr>
<td></td>
<td>• Clinically significant localization (intracranial, intraspinal, intraocular, cardiac tamponade, intra-articular, intramuscular with the development of compression syndrome, and retroperitoneal bleeding)</td>
</tr>
<tr>
<td></td>
<td>• Fatal bleeding</td>
</tr>
</tbody>
</table>

| 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 |

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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, alginate, 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.

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