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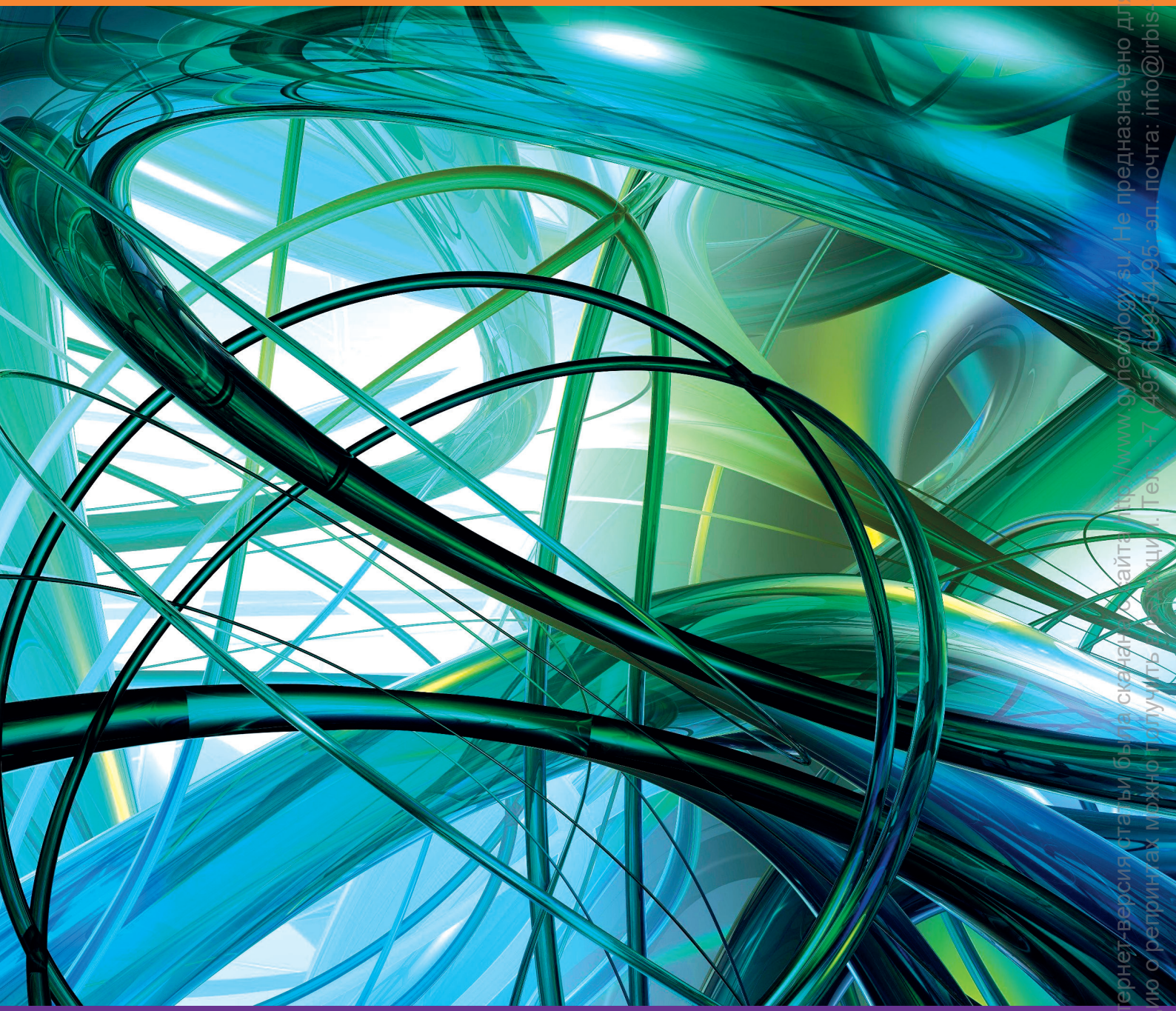

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Anticoagulants: dose control methods and inhibitors

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Abstract

These days, anticoagulants are in great demand. They are used as a prophylaxis for thromboembolic complications in various diseases and conditions in general therapeutic practice, cardiology, neurology, as well as obstetrics to manage high-risk pregnancies. The relevance of anticoagulants competent use has come to the fore in connection with the emergence of a new disease – COVID-19 and its serious complications such as developing thrombotic storm, in which the timely applied anticoagulant therapy is the key to the success of therapy. The risk of bleeding should be considered when using any anticoagulant. Age, impaired renal function and concomitant use of antiplatelet agents are common risk factors for bleeding. Moreover, only vitamin K antagonists and heparin have specific antidotes – vitamin K and protamine, respectively. Inhibitors of other anticoagulants are universal presented as inactivated or activated prothrombin complex concentrate and recombinant factor VIIa. Hemodialysis effectively reduces dabigatran concentration, activated charcoal is effective in the case of recent oral administration of lipophilic drugs. Research on new antidotes of currently available anticoagulants is under way, similar to testing of new types of anticoagulants that are sufficiently effective in preventing and treating thromboembolic complications with minimal risk of hemorrhagic. The main contraindication to anticoagulants use is the doctor's ignorance of the mechanisms of drug action and opportunities for suppressing its effect.

Keywords: bleeding, antidote, direct thrombin inhibitors, factor Xa inhibitors, warfarin, heparin, low molecular weight heparins, anticoagulants

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Антикоагулянты: методы контроля дозы и ингибиторы

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Резюме

Антикоагулянты – крайне востребованные препараты в наши дни. Они используются в качестве профилактики тромбоэмболических осложнений при различных заболеваниях и состояниях в общетерапевтической практике, в кардиологии, неврологии, а также в акушерстве при ведении беременности высокого риска. Актуальность вопроса грамотного использования антикоагулянтов вышла на передний план в связи с появлением нового заболевания – коронавирусной инфекции COVID-19 и ее серьезных осложнений в виде развития тромботического шторма, при котором своевременное назначение антикоагулянтной терапии является залогом успеха терапии. Риск кровотечения следует учитывать при использовании любых антикоагулянтов. Пожилой возраст, нарушение функции почек и одновременный прием антиагрегантов являются общими факторами риска кровотечений. При этом лишь для антагонистов витамина К и гепарина имеются специфические антидоты – витамин К и протамин, соответственно. Ингибиторы остальных антикоагулянтов универсальны – это неактивированный или активированный концентрат протромбинового комплекса и рекомбинантный фактор VIIa. Гемодиализ эффективно снижает концентрацию дабигатрана, активированный уголь эффективен в случае недавнего перорального приема липофильных препаратов. Исследования новых антидотов имеющихся в настоящее время антикоагулянтов продолжаются, также как испытания новых видов антикоагулянтов, обладающих достаточной эффективностью в профилактике и лечении тромбоэмболических осложнений при минимальном риске геморрагических. Основным противопоказанием к использованию антикоагулянтов является незнание врачом механизмов действия препарата и возможности подавления его эффекта.

Ключевые слова: кровотечение, антидот, прямые ингибиторы тромбина, ингибиторы Ха фактора, варфарин, гепарин, низкомолекулярные гепарины, антикоагулянты

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Highlights

What is already known about this subject?

- Anticoagulants are highly demanded today for prevention of thromboembolic complications in various diseases, both in general therapeutic practice as well as cardiology, neurology, and obstetrics.
- The risk of bleeding should be considered when using any anticoagulant. Common risk factors for bleeding are advanced age, impaired renal function, and concomitant use of antiplatelet agents.

What are the new findings?

- All data currently known on the safe use of all types of anticoagulants, the relevance of which has become especially acute in connection with the emergence of a new coronavirus infection COVID-19, are detailed and structured.
- Both actively used drugs and those that have recently begun to be used, as well as drugs at the stage of clinical trials, are presented.

How might it impact on clinical practice in the foreseeable future?

- The main contraindication to anticoagulants use is the doctor's ignorance of the mechanisms of drug action and opportunity for suppressing its effect. Deepening and expanding knowledge in this matter will increase effectiveness of clinical practice.

Основные моменты

Что уже известно об этой теме?

- Антикоагулянты крайне востребованные в наши дни в качестве профилактики тромбоэмболических осложнений при различных заболеваниях как в общетерапевтической практике, так и в кардиологии, неврологии, акушерстве.
- При использовании любых антикоагулянтов следует учитывать риск кровотечения. Общими факторами риска кровотечений являются пожилой возраст, нарушение функции почек и одновременный прием антиагрегантов.

Что нового дает статья?

- Подробно изложены и структурированы все данные, известные в настоящее время о безопасном использовании всех видов антикоагулянтов, актуальность которых особенно остро встала в связи с возникновением новой коронавирусной инфекции COVID-19.
- Представлены как активно используемые препараты, так и те, что недавно начали применяться, а также препараты на стадии клинических исследований.

Как это может повлиять на клиническую практику в обозримом будущем?

- Основным противопоказанием к использованию антикоагулянтов является незнание врачом механизмов действия препарата и возможности подавления его эффекта. Углубление и расширение знаний в этом вопросе повысит эффективность клинической практики.

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Introduction / Введение

Bleeding is the main side effect of any anticoagulant therapy. The risk of developing intracranial hemorrhage, gastrointestinal or uterine bleeding often leads the patient to refuse treatment.

In clinical trials regarding using vitamin K antagonists (VKAs) in patients with atrial fibrillation, the mean rate of major bleeding was 2.1 per 100 patient-years [1]. While using direct oral anticoagulants, the significant bleeding risk was 30 %, apixaban – 38 % compared with warfarin [2]. Patients with venous thromboembolism (VTE) differ from those with atrial fibrillation in bleeding risk factors: age, combination with antiplatelet therapy, concomitant oncological diseases, starting doses of anticoagulants. In patients receiving unfractionated heparin (UFH) the risk of bleeding depends on the patient baseline characteristics, surgery or trauma in the near past, dose of heparin, use of other antithrombotic drugs [3]. Randomizedand controlled trials comparing low molecular weight heparin (LMWH) or UFH with fondaparinux have shown a similar risk of major bleeding (1–2 % patients) [4]. The gastrointestinal tract is the most common source of bleeding while taking oral anticoagulants. For a long time VKAs have been used to treat and prevent venous and arterial thrombosis. In recent years new oral anticoagulants (NOACs) have been widely used. Some advantages over VKAs include more predictable pharmacokinetics and pharmacodynamics, less influence of drug interactions and eating behavior, and no need for regular monitoring as well as using fixed doses. However, unlike warfarin, this group of drugs have no specific inhibitors, making their use uncontrollable if it is necessary to quickly cancel the anticoagulant action due to the development of bleeding or if surgical treatment is required. In addition, compared to VKAs oral factor Xa (FXa) inhibitors cause menorrhagia at higher rate reaching up to 30 % of women [5]. This situation can be corrected with hormonal therapy, tranexamic acid, or drug withdrawal to return to warfarin use. The search for anticoagulants with a less risk of bleeding became essential for safety and improving patient compliance.

Anticoagulants. Mechanisms of action / Механизмы действия различных антикоагулянтов

Vitamin K antagonists / Антагонисты витамина К

Vitamin K antagonists inhibit the vitamin K regeneration. Vitamin K is a cofactor in reactions of gamma-carboxylation of factors II, VII, IX, X, proteins C, S, and Z. The pharmacokinetics and pharmacodynamics of VKAs have been studied in detail [6]. Genetic variation in P450 cytochrome and vitamin K epoxide reductase, drug interactions, food intake have an impact on the anticoagulant effects of warfarin. In this regard, taking warfarin should be accompanied by constantly monitored the international normalized ratio (INR). The results of previous studies have not demonstrated the effectiveness of genotyping while selecting dose of warfarin and optimizing warfarin therapy [7].

Heparins / Гепарины

Unfractionated heparin represents a mixture of sulfated glycosaminoglycans of various molecular weights that inhibit several factors of coagulation after binding to antithrombin. This process causes conformational changes with a 1000-fold increased inhibition efficiency. LMWH is obtained by UFH fractionation or depolymerization. It predominantly suppresses FXa. Fondaparinux is a pentasaccharide. Fondaparinux by binding to antithrombin enhances its effect in suppressing FXa. After intravenous injection, UFH half-life comprises 1–2 hours. The half-life of various LMWHs varies from 3 to 12 hours. Pharmacokinetic and biophysical properties of heparin limit its use [8]. Pharmacokinetic limitations are associated with various anticoagulant effects of heparins. These effects linked to antithrombin-independent binding of heparin to plasma proteins as well as endothelial and platelet proteins. Biophysical restrictions are presented by heparin-induced thrombocytopenia and osteopenia, which are less pronounced for LMWHs.

Direct oral thrombin inhibitors / Прямые оральные ингибиторы тромбина

Thrombin plays a crucial role in the coagulation cascade. It activates the protein C pathway, platelets, clotting factors, endothelial receptors and promotes the conversion of fibrinogen to fibrin. Ximelagatran was the first oral drug developed. Subsequently it was discontinued due to severe liver side effects [9]. Dabigatran etexilate is a prodrug lacking the risk profile of its predecessor. The bioavailability of dabigatran is 6.5 %. The half-life of dabigatran is 12–17 hours under normal renal function, and the maximum concentration is reached in plasma within 1.5–3 hours after ingestion. The kidneys excrete 80 % and 35 % of plasma proteins [10]. Dabigatran has demonstrated efficacy comparable to enoxaparin in preventing the risk of thrombosis in the postoperative period after hip [11] and knee [12]

arthroplasty. Its efficacy was comparable to that of warfarin in acute care [13] and prolonged maintenance therapy for VTE [14]. Studies have shown that dabigatran was as effective as warfarin in preventing stroke in patients with atrial fibrillation [15]. Dabigatran is currently approved in Europe and North America for the prevention of ischemia and stroke in patients with atrial fibrillation (stroke prophylaxis in atrial fibrillation, SPAF), as well as the VTE prevention after orthopedic surgery.

Oral Xa factor inhibitors / Оральные ингибиторы фактора Xa

The first drugs in this group, rivaroxaban and apixaban, act by reversibly blocking an active site of FXa. Bioavailability of them is higher than for dabigatran (edoxaban – 50 %, rivaroxaban – 80 %, apixaban – 60 %). After 1–4 hours peak concentrations are reached. The effect of drugs less depends on kidney function [16]. Studies in patients after orthopedic surgery, rivaroxaban vs. enoxaparin demonstrated higher efficacy of thromboprophylaxis with similar bleeding rate [17]. Its efficacy was also comparable to warfarin with VTE [4] and atrial fibrillation [18]. The drug is approved for thromboprophylaxis in orthopedic surgery to treat SPAF and VTE. Apixaban vs. enoxaparin has also been evaluated in patients undergoing knee [19] and hip [20] replacement surgery. It is equally effective at significantly lower bleeding rates. In studies, apixaban was more effective than acetylsalicylic acid (ASA) or warfarin in preventing stroke in patients with atrial fibrillation, with superior (vs. warfarin) [21] or similar (vs. ASA) [15] safety profile. It had lower bleeding rate and was non-inferior to warfarin in VTE treatment [22]. After orthopedic surgery, apixaban is approved for VTE prevention and SPAF (North America, Europe). Edoxaban is also approved as an alternative to warfarin for the treatment of VTE [23] and atrial fibrillation [24] with a significantly lower bleeding rate.

Factor XIa inhibitors / Ингибиторы фактора XIa

Factor XIa is an actively studied potential target for anticoagulant therapy. The FXIa inhibitors may be perfect for patients with a high risk of bleeding (dialysis patients with renal insufficiency). FXI is a part of the intrinsic pathway (contact-activated) of coagulation, being required for thrombus stabilization and growth [25]. FXI can be activated by both FXIIa and thrombin [26] via a positive feedback amplification loop (**Figure 1**) [27].

Congenital deficiency of FXI is found rarely in the general population (about 1 in 1,000,000) and is most common in the Ashkenazi Jewish community [28]. This deficiency is characterized by mild hemorrhagic diathesis showing no correlation with plasma FXI concentration [29]. Spontaneous bleeding due to its deficiency was not observed, distinguishing it from the deficiency of FXI, FVIII, FIX. Rarely, spontaneous bleeding also occurs, usually after surgery or trauma in tissues with high fibrinolytic activity, such as the mouth, nose and urinary tract.

Studies have shown that FXI deficiency is associated with reduced incidence of VTE and cardiovascular events (transient ischemic attack, stroke, and myocardial infarction) [30]. Individuals with lower plasma concentrations of FXI due to genetic predisposition have a 22 % reduced risk of ischemic stroke and venous thrombosis without an increased risk of bleeding [31].

Several FXIa and FXI inhibitors are currently under study (**Table 1**). The FXIa and FXI inhibitors examined in clinical trials include the monoclonal antibodies osocimab, the antisense oligonucleotide BAY 2976217 (IONIS FXI-LRx), abelacimab, xisomab 3G3 (AB023), the small molecules BMS-986177 and BAY 2433334. Small molecule inhibitors are believed to have low renal clearance (8–20 %), monoclonal antibodies and antisense oligonucleotides are not excreted by the kidneys which provide additional benefits for patients with renal insufficiency on hemodialysis [32]. Dialysis does not remove antisense oligonucleotides or monoclonal antibodies, and there is no evidence that dialysis removes small specific molecule inhibitors. They are highly protein-bound, this fact makes the process unlikely.

There was a dose-dependent reduction in the risk of venous and arterial thrombosis, while using an antisense oligonucleotide (IONIS-FXI Rx), without increasing bleeding time in mouse models [33]. In addition, IONIS-FXI Rx administration in baboon models leads to a sustained antithrombotic effect without increased bleeding [34]. In a phase 2 IONIS-FXI Rx, there has been studied patients after elective unilateral knee arthroplasty [35]. Patients for 35 days before surgery received IONIS-FXI Rx, 300 or 200 mg enoxaparin (LMWH). IONIS-FXI Rx 300 mg (200 mg dose was non-inferior to enoxaparin) was superior to enoxaparin in reducing VTE. Doses of IONIS-FXI Rx were associated with fewer bleeding events [35].

BAY 2976217 is a ligand-conjugated version of IONIS-FXI Rx (also known as FXI-LICA and IONIS-FXI-LRx). The tolerability, safety, pharmacodynamics, and pharmacokinetics of BAY 2976217 were investigated in healthy volunteers in double-blind, placebo-controlled study phase 1 trial [36].

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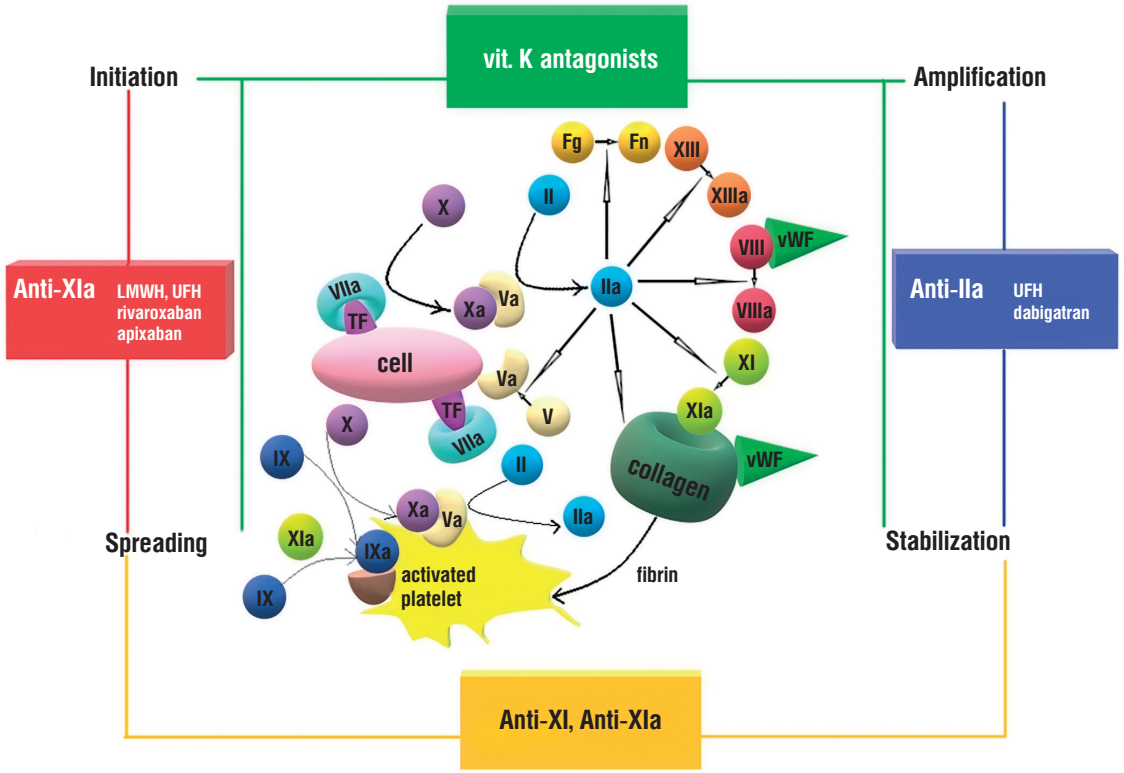

Figure 1. Anticoagulant application sites [27].

Note: *vWF – von Willebrand factor; TF – tissue factor; vit. K – vitamin K; Anti-IIa, Anti-Xa, Anti-XI, Anti-XIa – antagonists of IIa, Xa, XI, XIa factors; LMWH – low molecular weight heparin; UFH – unfractionated heparin; Fg – fibrinogen; Fn – fibrin.*

Рисунок 1. Точки приложения антикоагулянтов [27].

Примечание: *vWF – фактор фон Виллебранда; TF – тканевой фактор; вит. К – витамин К; Anti-IIa, Anti-Xa, Anti-XI, Anti-XIa – антагонисты факторов IIa, Xa, XI, XIa; LMWH – низкомолекулярный гепарин; UFH – нефракционированный гепарин; Fg – фибриноген; Fn – фибрин.*

Table 1. Factors XI and XIa inhibitors under development.

Таблица 1. Разрабатываемые препараты ингибиторов XI и XIa факторов.

Name / Название	Type / Тип
BMS-986177 Mikveksian BMS-986177 Миквексиан	Low molecular weight inhibitor of factor XIa Низкомолекулярный ингибитор фактора XIa
BAY 2433334 Asundexian BAY 2433334 Асундексиан	Low molecular weight inhibitor of factor XIa Низкомолекулярный ингибитор фактора XIa
Xisomab 3G3 AB023 Ксисомаб	Low molecular weight inhibitor of factor XIa Низкомолекулярный ингибитор фактора XIa
Osocimab Осоцимаб	Monoclonal antibody to factor XI Моноклональное антитело к фактору XI
Abelacimab Абелацимаб	Monoclonal antibody to factor XIa Моноклональное антитело к фактору XIa
IONIS-FXI Rx	Monoclonal antibody to factors XI/XIa Моноклональное антитело к факторам XI/XIa
BAY 2976217 (FXI-LICA)	Factor XI antisense oligonucleotide Антисмысловой олигонуклеотид фактора XI

Osocimab (BAY 1213790), the anti-FXIa antithrombotic antibody, demonstrated antithrombotic effects without increasing bleeding time in a rabbit model of arterial thrombosis. In a study, administration of abelacimab, the dual FXIa/FXI monoclonal antibody, reduced VTE by up to 5 % (75 mg dose) and 4 % (150 mg dose) compared with 22 % in patients receiving 40 mg enoxaparin daily within 30 days after a total knee

replacement. 30 mg of abelacimab was non-inferior (VTE in 13 %) to enoxaparin [37].

FXI inhibitors may improve the safety record compared to other oral anticoagulants. In the FOXTROT study, osocimab reduced minor bleeding (0–3 % of patients compared with 6 % in the group of enoxaparin) [38]. In phase 2 of another study, 3 % of patients treated with IONIS-FXI Rx developed clinically significant bleeding compared with 8 % of enoxaparin group. Studies have shown that dabigatran is less effective than warfarin in patients with mechanical heart valves [39]. In addition, decrease in FXI concentration *in vitro* reduces thrombin formation induced by mechanical valve [40].

A phase 2 multicenter study in patients with renal failure on hemodialysis showed that IONIS-FXI Rx reduced blood clotting at the dialysis membrane compared to heparin in standard regimens, however, these results require further research [41]. Thus, there is an opportunity to use new drugs that inhibit FXI in dialysis patients with renal failure, not only to prevent stroke in atrial fibrillation but more broadly to prevent cardiovascular complications.

Methods for controlling anticoagulants dose and monitoring hemorrhagic complications while using various anticoagulants / Методы контроля дозы антикоагулянтов и мониторинг на фоне геморрагических осложнений при использовании различных антикоагулянтов

Anticoagulant therapy is applied for at least 3 months after the first episode of thrombosis, whereas for patients at high risk of recurrent VTE long-term (possibly incessant) therapy is recommended [42]. Stratification of patients depending on the risk of recurrent VTE is carried out primarily with the determination of a fibrin breakdown product, D-dimer, and coagulation activation markers.

D-dimer / D-димер

D-dimer is a strategical indicator of activated coagulation and fibrinolysis and an indirect prothrombotic marker. D-dimer is formed due to sequential reactions involving thrombin, activated factor XIII (FXIIIa) and plasmin [43]. Thrombin, formed upon activation of coagulation, activates FXIII and converts fibrinogen to fibrin. FXIIIa binds D-domains in fibrin monomers. Formed on the surface of fibrin as a result of plasminogen activation, plasmin cleaves the fibrin substrate at certain positions. The D-dimer is synthesized during the cleavage of fibrin cross-linked with FXIIIa. The plasma D-dimer half-life is about 8 hours, being excreted predominantly by the reticuloendothelial system and kidneys. Residual concentrations of D-dimer can be found in the bloodstream in the normal state, while in any condition associated with increased fibrin formation and fibrinolysis pathologically elevated levels may be observed [43]. D-dimer concentration tests are best validated for the diagnostics and monitoring of disseminated intravascular coagulation as well as for exclusion of VTE.

High concentrations of D-dimer allow to identify a group of a high relapse risk, in which long-term anticoagulant therapy is justified [44]. Conversely, low concentrations of D-dimer distinguish a group of a low relapse risk, wherein long-term anticoagulant therapy may not be warranted [45]. Many clinical studies investigated and confirmed the use of D-dimer for this purpose. In most studies, the concentration of D-dimer was determined 3–4 weeks after the cessation of anticoagulant therapy. D-dimer was measured consistently during anticoagulation and at different times after anticoagulation was stopped in some studies [46]. One study it measured during anticoagulant therapy [47]. Monitoring the concentration of D-dimer during anticoagulant therapy is necessary to select a more correct and minimal dose of the drug, followed by assessing its effectiveness and safety.

Although the use of anticoagulants is associated with a risk of bleeding, anticoagulants increase survival in patients with severe infection COVID-19. Dose of anticoagulants is selected, among other parameters, according to the magnitude of increased concentration of D-dimer in patients with severe COVID-19.

In the case of developing hemorrhagic complications, an express test while using VKAs is INR. For NOACs, general measures of hemostasis parameters such as prothrombin time (PT), activated partial thromboplastin time (APTT), or thrombin time (TT), should be used, which can give a rough qualitative estimate of the effect, to a greater extent for dabigatran (with PT or APTT) or rivaroxaban (with PT) than for apixaban and edoxaban [48]. In the group of patients at high risk of thromboembolic complications, level of D-dimer may contribute additionally to account for resuming anticoagulant therapy, as well as drugs and doses to be used.

Bleeding. Definition of concepts / Кровотечение. Определение понятий

The definition given to massive bleeding by the International Society on Thrombosis and Hemostasis (ISTH) has been widely used in the last decade [49]. There are other types of classifications of bleeding

severity. In most definitions, the main criterion is provided by decline in hemoglobin. A number of authors separately distinguish a life-threatening bleeding. There is also a separate group of bleeding – clinically relevant non major bleeds (CRNMBs) corresponding to moderate and minor bleeding (**Table 2**).

Bleeding frequency and risk factors for bleeding under anticoagulant therapy / Частота кровотечений и факторы риска кровотечений при приеме антикоагулянтов

Vitamin K antagonists / Антагонисты витамина К

Regardless of the therapeutic dose used and the choice of anticoagulant, a risk of bleeding is always present. VKAs use increases the risk of intracranial hemorrhage by about 0.2 % per year and the risk of significant bleeding by 2–3 % per year [51]. The main risk factors for bleeding during anticoagulant therapy include high anticoagulant doses, concomitant use of other drugs that affect hemostasis, such as antiplatelet agents, anti-inflammatory non-steroidal drugs or cyclooxygenase inhibitors, characteristics of patient (age and comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease, ischemic stroke, renal failure, liver disease, alcoholism, malignancy), and therapy duration [52].

Heparins / Гепарины

The significant bleeding risk due to heparins ranges from 0 to 2% [52] depending on the dose of anticoagulants, the underlying disease, or taking other anticoagulants. Renal insufficiency, age, and gender of the patient are also considered as risk factors for heparin-induced bleeding [52]. LMWHs in patients with impaired renal function should be used with caution, as drug bioaccumulation may lead to bleeding [53]. Prophylactic doses of fondaparinux 2.5 mg daily are associated with minor bleeding than therapeutic LMWHs doses [54] and the same risk as UFH [55] or prophylactic LMWHs doses [56].

New generation anticoagulants / Новые антикоагулянты

NOACs have a wider therapeutic window and a shorter half-life. Theoretically, predictive risk factors for bleeding for VKAs apply as well to NOACs. Renal failure is an essential indicator, given that drugs are removed from the body via kidneys. Age is an independent risk factor [57]. Studies have shown that dabigatran applied at dose 150 mg twice a day was associated with a higher rate of bleeding than 110 mg twice daily [58]. The incidence of severe bleeding was 3.74 and 2.99% per year at a dose of 150 mg and 110 mg, respectively. The risk of bleeding increases dramatically when dabigatran and warfarin are combined with antiplatelet agents [59]. Data analysis on rivaroxaban use in patients with atrial fibrillation showed

Table 2. Bleeding characteristics [49, 50].

Таблица 2. Характеристика кровотечений [49, 50].

Type of bleeding / Вид кровотечения	ISTH characteristics / Характеристики ISTH
Bleedings outside of surgery / Кровотечения вне оперативных вмешательств	
Massive bleedings Массивные кровотечения	– severe bleeding; – выраженное кровотечение; – decrease in hemoglobin concentration by 20 g/l and more; – снижение концентрации гемоглобина на 20 г/л и более; – need for 2 or more doses of RBC mass/whole blood – потребность в ведении 2 и более доз эритромассы/цельной крови
Clinically relevant non major bleeds (CRNMBs) Незначительные/умеренные кровотечения	– bleeding requiring medical attention; – кровотечение, требующее врачебного вмешательства; – bleeding requiring hospitalization – кровотечение, требующее госпитализации
Bleedings as a result of surgery / Кровотечения как результат оперативных вмешательств	
Massive bleedings Массивные кровотечения	– severe bleeding; – выраженное кровотечение; – source of bleeding inside or outside of the operated organ; – источник кровотечения внутри или вне оперируемого органа; – decrease in hemoglobin concentration by 20 g/l and more; – снижение концентрации гемоглобина на 20 г/л и более; – need for 2 or more doses of RBC mass/whole blood; – потребность в ведении 2 и более доз эритромассы/цельной крови; – bleedings requiring reoperation; – кровотечения, требующие повторного оперативного вмешательства; – unstable hemodynamics – нестабильная гемодинамика

that risk factors for bleeding due to such therapy were presented by high body mass index, older age, diabetes mellitus, male sex, and low clearance of creatinine [60].

Anticoagulant therapy and correction of its hemorrhagic complications / Коррекция геморрагических осложнений на фоне антикоагулянтной терапии

The correction approach of hemorrhagic complications after using anticoagulants should be personalized in each specific case, with a balance between the risk of thromboembolic complications, indications for anticoagulation and severity of bleeding, as well as the degree of clinical urgency and indications for the complete drug withdrawal. **Table 3** summarizes main characteristics of the anticoagulants on the market and agents used to combat hemorrhagic complications.

Methods for correcting hemorrhagic complications upon using vitamin K antagonists / Способы коррекции геморрагических осложнений на фоне использования антагонистов витамина К

Vitamin K / Витамин К

Vitamin K is inexpensive, reliable, effective and safe warfarin antidote. It can be used either intravenously or orally [61]. Oral vitamin K at doses of 1 to 2.5 mg lowers the INR within 24 hours for non-bleeding patients with an INR > 4 [62]. Oral intake of vitamin K is also possible in patients with an INR of 5–8, despite the high risk of bleeding. Bleeding developed while taking warfarin, 2.5 mg of vitamin K leads to normal INR in most patients. Only some patients have to increase the dose up to 10 mg with very high INR levels or concomitant liver dysfunction (**Table 4**).

Although both intravenous and oral forms of vitamin K are effective equally in correcting INR within 24 hours, the intravenous form can do so within 6 to 8 hours [63]. In this regard, some recommendations for massive bleeding include an intravenous route using of vitamin K 5 to 10 mg as a slow infusion (over 30 minutes) after using warfarin in combination with prothrombin complex concentrate (PCC) [64]. The effectiveness of combined use is achieved because PCC introduction provides a temporary correction of INR due to the short half-life of vitamin K-dependent clotting factors, particularly FVII (6 hours). Supplementation with vitamin K further provides a long-term correction of INR by restoring hepatically produced clotting factors. Moreover, the use of vitamin K at high doses is associated with developing transient VKAs resistance and subsequently complicated reach of therapeutic range INR values.

Fresh frozen plasma, prothrombin complex concentrate / Свежезамороженная плазма, концентрат протромбинового комплекса

Rapid hemostasis correction during bleeding resulting from warfarin can be achieved by introducing functionally active blood coagulation factors. Fresh frozen plasma (FFP) is an affordable product containing vitamin K-dependent clotting factors. It is used in large volumes (> 1500 ml) to ensure a marked increase in clotting factors in case of ongoing bleeding during warfarin withdrawal. However, in elderly patients it might be problematic to rapidly inoculate large volumes. The danger is also posed by potential transmission of several infections with donor plasma. Unlike FFP, PCC contains factors VII, X, IX, and II at about 25 times higher concentration, which significantly reduces the total infusion volume, minimizes the risk of transfusion-related circulatory overload, and accompanying lung injury [65]. There are two types of PCC products. Three-factor PCC contains a smaller amount of VII factor. Studies have shown that three-factor PCC cannot sufficiently reduce INR due to a lower concentration of factor VII. The additional use of FFP and a three-factor PCC provides a more significant reduction in INR [66]. The effectiveness of four-factor PCC with a higher concentration of factor VII is much higher, but potential subsequent thrombotic complications should be taken into account [67].

Recombinant factor VIIa / Рекомбинантный фактор VIIa

Few studies have examined the use of recombinant factor VIIa (rVIIa) with warfarin in bleeding. One of these, retrospective trial showed that rVIIa rapidly normalized INR without influencing mortality rates [68]. Moreover, the incidence of thromboembolic complications was higher compared with standard therapy. Another retrospective study showed an advantage rVIIa vs. PCC in correcting INR in intracranial hemorrhage treated with warfarin [69]. A meta-analysis has shown that the use of high-dose rVIIa significantly increases the arterial but not venous risk of thromboembolic events, primarily in elderly patients [70]. Given the conflicting and limited data on potential risk, the question of using rVIIa in the treatment of bleeding along with warfarin remains open.

Activated prothrombin complex concentrate / Активированный концентрат протромбинового комплекса

Retrospective studies examining the use of activated PCC in managing hemorrhagic complications along with warfarin showed that this method is more effective than FFP in reducing INR, showing no significant difference

Table 3. Anticoagulants and their antidotes.

Таблица 3. Антикоагулянты и их антидоты.

Drug **Препарат**	**Site of action** **Точка приложения**	**Laboratory test** **Лабораторный мониторинг**	**Half-life** **Время полувыведения**	**Preferred route of excretion** **Преимущественный путь выведения**	**Antidote** **Антидот**
Vitamin K antagonists Антагонисты витамина К	Synthesis of vitamin K-dependent coagulation factors Синтез витамин К-зависимых факторов свертывания [51]	INR (PT) МНО (ПВ)	20–60 h (average 36–48 h) 20–60 ч (в среднем 36–48 ч)	Metabolism in the liver, excretion of metabolites by the kidneys Метаболизм в печени, выведение метаболитов почками	Vitamin K Витамин К PCC КПК aPCC аКПК FFP СЗП [52]
Unfractionated heparin (UFH) Нефракционированный гепарин (НФГ)	Factor IIa Фактор IIa Factor Xa Фактор Xa Antithrombin Антитромбин [52]	APTT АЧТВ	1–2 h 1–2 ч	Kidney Почки	Protamine sulfate Протамина сульфат [55]
Low molecular weight heparin (LMWH) – enoxaparin Низкомолекулярный гепарин (НМГ) – эноксапарин	Factor Xa Фактор Xa [53]	Anti-Xa activity Анти-Xa активность [54]	3–13 h (average 3–7 h) 3–13 ч (в среднем 3–7 ч)	Kidney Почки	Protamine sulfate rVIIa Протамина сульфат pVIIa [56]
Fondaparinux Фондапаринукс	Factor Xa Фактор Xa	Anti-Xa activity Анти-Xa активность	17–21 h 17–21 ч	Kidney Почки	rVIIa / pVIIa [8]
Dabigatran Дабигатран	Factor IIa Фактор IIa [58]	APTT АЧТВ TT ТВ	12–17 h 12–17 ч	80 % kidney 80 % почки	aPCC аКПК FFP СЗП Idarucizumab Идаруцизумаб [59]
Rivaroxaban Ривароксабан	Factor Xa Фактор Xa [60]	PT ПВ Anti-Xa activity Анти-Xa активность	9–15 h 9–15 ч	66 % kidney 66 % почки	FFP СЗП aPCC аКПК Andexanet alfa Андексанет альфа rVIIa / pVIIa
Apixaban Апиксабан	Factor Xa Фактор Xa	Anti-Xa activity Анти-Xa активность	8–15 h 8–15 ч	25 % kidney 25 % почки	FFP СЗП aPCC аКПК Andexanet alfa Андексанет альфа rVIIa / pVIIa [22]
Edoxaban Эдоксабан	Factor Xa Фактор Xa	Anti-Xa activity Анти-Xa активность PT ПВ [32]	6–11 h 6–11 ч	35 % kidney 35 % почки	FFP СЗП aPCC аКПК Andexanet alfa Андексанет альфа rVIIa / pVIIa [24]

Note: *INR – international normalized ratio; APTT – activated partial thromboplastin time; PT – prothrombin time; TT – thrombin time; PCC – prothrombin complex concentrate; aPCC – activated prothrombin complex concentrate; FFP – fresh frozen plasma; rVIIa – recombinant factor VIIa.*

Примечание: *МНО – международное нормализованное отношение; АЧТВ – активированное частичное тромбопластиновое время; ПВ – протромбиновое время; ТВ – тромбиновое время, КПК – концентрат протромбинового комплекса; аКПК – активированный концентрат протромбинового комплекса; СЗП – свежезамороженная плазма; pVIIa – рекомбинантный фактор VIIa.*

Table 4. Recommendations on usage and dosage of vitamin K for under varying international normalized ratio (INR) [49, 52].

Таблица 4. Рекомендации по использованию и дозированию витамина К при различных значениях международного нормализованного отношения (МНО) [49, 52].

INR / МНО	Tactics / Тактика	Dose of vitamin K / Доза витамина К
Above therapeutic values but below 4.5 Выше терапевтических значений, но ниже 4,5	Снижение дозы варфарина под лабораторным контролем до терапевтических значений МНО Reducing the dose of warfarin under laboratory control to therapeutic INR values	Not used Не используется
4,5–10	Снижение дозы варфарина под лабораторным контролем до терапевтических значений МНО Reducing the dose of warfarin under laboratory control to therapeutic INR values	In patients at high risk of bleeding, 1–2 mg orally У пациентов с высоким риском кровотечения 1–2 мг перорально
Over 10 Более 10	Without canceling warfarin, take vitamin K under the control of INR, repeat the intake of vitamin K according to indications Не отменяя варфарин, принять витамин К под контролем МНО, повторить прием витамина К по показаниям	2.5–5.0 mg orally at a time 2,5–5,0 мг перорально за один прием

in survival rate [71]. However, while using this group of drugs, an increased risk of thromboembolic complications was also noted.

Methods for correcting hemorrhagic complications during heparins' therapy / Способы коррекции геморрагических осложнений на фоне использования гепаринов

Protamine sulfate / Протамина сульфат

Protamine sulfate is an alkaline positively charged protein derived from fish sperm. It completely abrogates the anticoagulant effect due to complexing with negatively charged and acidic heparin [72]. For almost 30 years, protamine sulfate has been widely used for hemorrhagic complications associated with the use of UFH. Protamine sulfate at a dose of 1 mg/100 units of heparin inhibits the action of UFH, while it just partially neutralizes other heparinoids such as danaparoid or LMWHs, because protamine sulfate affects the suppression of FIIa (thrombin). Protamine sulfate has a very short half-life (about 7 minutes). Repeated doses of protamine sulfate may be required to altogether abolish UFH, with a maximum dose of 50 mg [3]. To monitor efficacy APTT may be used [3]. Protamine sulfate affects anti-Xa activity with LMWHs only partially (60–80 %) [73]. Thus, even if the APTT is fully normalized after administration of protamine, measurement of anti-Xa activity is necessary [73].

The use of protamine sulfate has been associated in cardiovascular surgery with an increased risk of anaphylaxis, in around 1% cases secondary to histamine release [74]. The development of thrombocytopenia has also been described while using it [75]. A study has shown that its use can result in the antibodies against protamine and heparin, which activate platelets being associated with episodes of thrombocytopenia and an increased risk of thromboembolism in cardiac surgery [76].

Protamine sulfate causes hypersensitivity reactions, including anaphylaxis, in fish allergic patients with previous exposure to protamine-containing drugs or protamine such as insulin [72]. Patients with a verified allergy to protamine sulfate should be treated in advance with steroids and antihistamines [77].

Recombinant factor VIIa / Рекомбинантный фактор VIIa

A large number of studies demonstrate that rVIIa is effective in the correction of hemorrhagic complications due to LMWHs [78, 79], idraparinux [80] or fondaparinux [81]. In these trials, 90 μg/kg was the dose at which a positive clinical effect was achieved. Recombinant VIIa is also effective in LMWHs overdosage in patients with pre-existing hypercoagulation and/or acute VTE [82].

Methods for correcting hemorrhagic complications during pentasaccharides use / Способы коррекции геморрагических осложнений на фоне использования пентасахаридов

Fondaparinux is the only pentasaccharide-based anticoagulant used to treat and prevent VTE that binds to antithrombin, and inhibits selectively FXa [79, 83]. Protamine is ineffective against the anticoagulant effects of fondaparinux. Pentasaccharides have no specific antidotes. Hemodialysis can reduce the plasma concentration of fondaparinux by about 20 %. Recombinant VIIa is effective in healthy volunteers and *in vitro* studies [84, 85]. However, thromboembolic complications remain a problem for using rVIIa in approximately 7 % of patients.

Methods for correcting hemorrhagic complications after using new oral anticoagulants / Способы коррекции геморрагических осложнений на фоне использования новых оральных антикоагулянтов

Management of the hemostasis system in the setting of NOACs should be personalized in based on severity of bleeding, indications for anticoagulation, patient characteristics such as age, comorbidities, time after the last dose, drug dose, and location of bleeding. While using NOACs, a standard treatment and examination regimen should be followed up in patients with bleeding, including adequate fluid therapy and oxygenation, hemostasis laboratory assessment, and general clinical parameters, such as creatinine and complete blood count. APTT is dependent on the concentration of dabigatran. Normal APTT values preclude the use of NOACs as the bleeding cause. Normal PT value excludes rivaroxaban as a hemorrhage cause [86].

Simply discontinuing NOACs may be sufficient for minor bleeding in patients with normal renal function, given the short half-life of the drugs. According to indications, it is necessary to stop the combined use of antiplatelet agents and anticoagulants to begin introduction of specific or non-specific hemostatic agents. According to the indications, it is necessary to use other hemostatic measures, such as mechanical compression, surgical hemostasis, etc. It is also possible to use antifibrinolytic drugs to develop hemorrhagic complications due to NOACs.

Methods for correction of hemorrhagic complications due to direct thrombin inhibitors / Способы коррекции геморрагических осложнений на фоне использования прямых ингибиторов тромбина

Activated oral charcoal / Активированный уголь для перорального применения

Oral activated charcoal effectively absorbs up to 99.9 % of dabigatran [87]. It should be used dissolved in acidified water within 1–2 hours after taking the drug.

Hemodialysis / Гемодиализ

Since dabigatran is not actively bound to plasma proteins (35 %), it can potentially be removed from the circulation by hemodialysis in case of life-threatening bleeding, intoxication, or the need for surgical emergency treatment [88]. Studies have shown that up to 59.3 % of dabigatran is eliminated within 4 hours of hemodialysis [89]. However, the need to create central venous access with large diameter catheters in patients on anticoagulant therapy is an additional risk factor and a limitation of this strategy.

Prothrombin complex concentrate and activated prothrombin complex concentrate / Концентрат протромбинового комплекса и активированный концентрат протромбинового комплекса

Several studies have demonstrated PCC effectiveness in the treatment of hemorrhagic complications associated with dabigatran in mice, rats, and rabbits [90]. In studies involving healthy male volunteers, no reliable data on PCC effectiveness along with complications of dabigatran were found [91]. Therefore, no evidence is available regarding effectiveness of PCC in the dabigatran-related complications. At the same time, the use of activated PCC seems promising [92], as evidenced particularly by studies on gastrointestinal bleeding, intracranial hemorrhages due to dabigatran [93, 94]. An essential subject for further research is the increased risk of thrombotic complications associated with using activated PCC.

Activated recombinant factor VIIa / Активированный рекомбинантный фактор VIIa

In mouse models, rVIIa has been shown to be effective with partial normalization of APTT in patients receiving dabigatran [95]. However, other animal model studies [90] and *ex vivo* rVIIa studies have not confirmed a neutralizing effect of dabigatran [92].

Idarucizumab / Идаруцизумаб

Idarucizumab, an antidote to dabigatran, is a fragment of a monoclonal Fab antibody that binds to dabigatran and alters its anticoagulant properties [96]. The antidote should be administered as a 5 g bolus dose intravenously and is approved for use in massive bleeding as well as when emergency surgical treatment is required to prevent massive intraoperative blood loss.

Methods for correcting hemorrhagic complications during therapy with factor Xa inhibitors / Способы коррекции геморрагических осложнений на фоне использования ингибиторов фактора Xa

The strategy for direct factor Xa inhibitors is similar to dabigatran, except that direct FXa inhibitors bind well to plasma proteins and are poorly removed from the circulation by hemodialysis.

Activated oral charcoal / Активированный уголь для перорального применения

No reliable data on the effectiveness of activated charcoal as an antidote for rivaroxaban are currently available. Studies have shown that the effect of apixaban can be interrupted by oral administration of activated charcoal in dogs even 3 hours after ingestion [97].

Prothrombin complex concentrate / Концентрат протромбинового комплекса

Animal studies have demonstrated the effectiveness of PCC in the hemorrhagic complications due to rivaroxaban and apixaban [98]. An *in vitro* study using human plasma has demonstrated the efficacy of PCC in normalizing laboratory parameters with rivaroxaban and apixaban [91, 99]. Two cohort prospective studies have evaluated the safety and efficacy of PCC for the major bleeding treatment in patients treated with rivaroxaban or apixaban [100, 101]. In the Swedish study, the drug's effectiveness was 69 % [100]. Most patients in the study had intracranial hemorrhages (61.5 %), two patients suffered from ischemic stroke developed within 30 days after drug correction. In the Canadian study, the effectiveness was 68 %; 8 % had a thromboembolic episode, and 14 % died within 30 days after applying this approach [100].

Activated prothrombin complex concentrate and activated recombinant factor VIIa / Активированный концентрат протромбинового комплекса и активированный рекомбинантный фактор VIIa

Activated PCC and activated rVIIa were effective after using edoxaban and rivaroxaban in animal models [91, 102].

Universal antidotes of new oral anticoagulants / Универсальные антидоты новых оральных антикоагулянтов

Andexanet alfa / Андексанет альфа

A new recombinant andexanet alfa protein (PRT064445 or PRT4445) structurally transforms the FXa by making it hemostatically inactive [103, 104]. An andexanet alfa is an inactive form of FXa that acts as a 'bait' by binding to and inhibiting FXa inhibitors as well as fondaparinux and LMWHs [105]. The drug effectiveness has been studied and confirmed only in patients with massive bleeding requiring no emergency surgery.

PER977 is another small synthetic molecule considered a potential antidote for several NOACs, including edoxaban, apixaban, rivaroxaban and dabigatran [106]. The candidate drug is effective in animal and *ex vivo* human plasma models.

Management of patients with hemorrhagic complications / Тактика ведения пациентов при геморрагических осложнениях

Fundamentals of bleeding control / Основные принципы борьбы с кровотечением

If hemorrhagic complications occur during anti-coagulant therapy, first of all, a detailed anamnesis should be collected from both the patient and close relatives. What anticoagulant was taken by a patient? When was the last time applied? Did the patient have kidney disease? Did patient also receive ASA or other drugs that suppress platelet function?

The main approaches to the treatment of hemorrhagic complications associated with using anticoagulants are similar to the basic principles of managing hemorrhagic complications of other etiologies (**Figure 2**). First of all, these are measures aimed at stopping or reducing bleeding, including local hemostasis (tamponade of the nasal cavity, compression in case of arterial bleeding, insertion of the Blakemore probe in case of bleeding from varicose veins of the esophagus when urgent endoscopy is unavailable), correcting consequences of blood loss (intravenous infusion therapy, oxygen therapy, blood transfusion, other types of hemodynamic support). For trauma-related bleeding tranexamic acid should be used [107]. At the same time, in hematuria tranexamic acid is contraindicated due to the risk of thrombogenesis in the ureter lumen and hydronephrosis. Any antiplatelet, anticoagulant agent and non-steroidal anti-inflammatory drug should be discontinued. Activated charcoal reduces the effect of all NOACs, and therefore can be used for several hours in case of bleeding due to an overdose or accidental use of such agents.

At the next stage, a comprehensive hemostasis assessment is required to select optimal therapy.

Intracranial hemorrhage / Внутричерепные кровоизлияния

Subdural or intracerebral hematoma evacuation should be performed only when effect of anticoagulant drug is finished after its complete withdrawal [108]. Along with preventing VTE, intermittent pneumatic compression should be used [108]. Prophylactic use of LMWHs and heparin in stable patients is possible 2–4 days after the bleeding episode [109]. The decision to resume full anticoagulation should be based on assessing the risk of recurrent intracranial hemorrhage and the risk of thromboembolic complications. Eight weeks is the optimal timing for resuming anticoagulant therapy, which has been studied with VKAs alone [110]: shorter for post-traumatic intracerebral hemorrhage [111], but longer for amyloid angiopathy or subdural hematoma (which has a higher risk of recurrence). For patients with warfarin-associated intracranial hemorrhage, switching to NOACs is possible due to their lower risk of developing intracranial hemorrhage. For patients with intracranial hematomas, while using NOACs, consideration should be given to resuming it at lower dose. In all cases,

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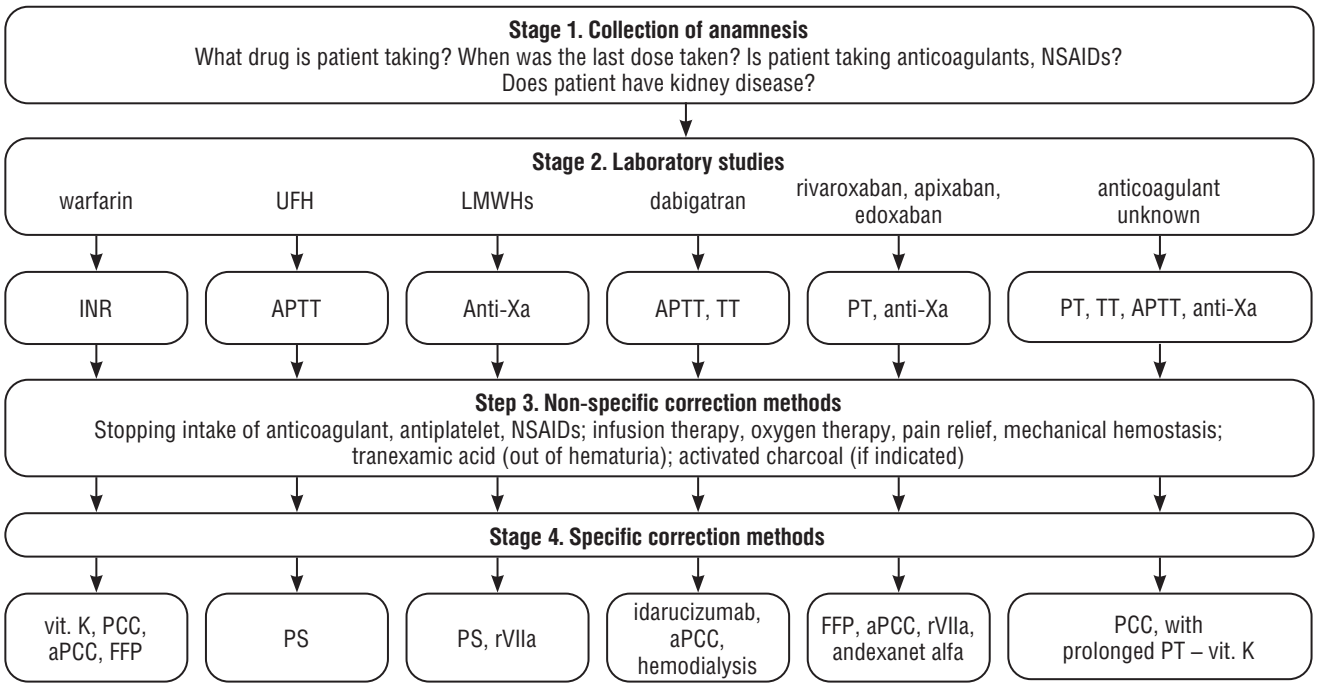

Figure 2. Strategy for managing hemorrhagic complications during antithrombotic therapy [drawn by authors].

Note: *UFH – unfractionated heparin; LMWHs – low molecular weight heparins; NSAIDs – non-steroidal anti-inflammatory drugs; INR – international normalized ratio; APTT – activated partial thromboplastin time; anti-Xa – anti-Xa activity; PT – prothrombin time; TT – thrombin time; vit. K – vitamin K; PCC – prothrombin complex concentrate; aPCC – activated prothrombin complex concentrate; FFP – fresh frozen plasma; PS – protamine sulfate; rVIIa – activated recombinant factor VIIa.*

Рисунок 2. Стратегия борьбы с геморрагическими осложнениями на фоне противотромботической терапии [рисунок авторов].

Примечание: *UFH – нефракционированный гепарин; LMWHs – низкомолекулярные гепарины; NSAIDs – нестероидные противовоспалительные средства; INR – международное нормализованное отношение; APTT – активированное частичное тромбопластиновое время; anti-Xa – анти-Xa активность; PT – протромбиновое время; TT – тромбиновое время; vit. K – витамин K; PCC – концентрат протромбинового комплекса; aPCC – активированный концентрат протромбинового комплекса; FFP – свежезамороженная плазма; PS – протамина сульфат; rVIIa – активированный рекомбинантный фактор VIIa.*

the decision should be preceded by a comprehensive laboratory hemostasis assessment, including assessing the concentration of plasma D-dimer.

Gastrointestinal bleeding / Желудочно-кишечные кровотечения

The gastrointestinal tract is the most common source of massive bleeding while taking anticoagulants, while gastrointestinal bleeding can be a marker of the tumor process. In this regard, endoscopic examination to identify the source of bleeding and stop it, are the first line measures in developed gastrointestinal bleeding. The latter can be achieved by coagulation, ablation, hemoclipping of very deep ulcers with a visible blood vessel, local administration of epinephrine, coagulation with argon plasma for angiodysplasia, or ectasia of the gastric antrum, ligation of esophageal varices and sclerotherapy [112]. In case of bleeding from a stomach ulcer, intravenous administration of a proton pump inhibitor is indicated. The use of anti-inflammatory non-steroidal drugs should be avoided. The optimal time to resume anticoagulation is within 3–6 weeks after an episode of upper gastrointestinal bleeding, after a detailed laboratory hemostasis assessment, including measuring D-dimer concentration [113]. Early resumption of anticoagulation therapy may be considered in case of high thromboembolism risk.

A multidisciplinary approach is required involving both a multi-field specialist and a hemostasis specialist, a cardiologist and/or neurologist for all hemorrhagic complications due to anticoagulant therapy, to optimize hemostatic treatment and the timing to start thromboembolism prevention.

Conclusion / Заключение

The complexity and versatility of antithrombotic therapy are growing with the advent of more and more advanced drugs. Bleeding is a formidable complication resulting from using any anticoagulant. Antidotes are a valuable addition to the arsenal of drugs used to treat hemorrhagic complications related to anticoagulants, but their importance should not be overestimated.

Randomized controlled trials have not confirmed their efficacy and safety. It all suggests that knowledge about the risk factors for development of hemorrhagic complications after taking various anticoagulants, indications for their use, features of monitoring their effectiveness and safety, as well as potential for complete abrogation of their action, if necessary, are essential for practicing physicians of various specialties.

New anticoagulants targeting coagulation factors XI and XII are undergoing clinical trials. Antibodies, antisense oligonucleotides, aptamers, polyanion antagonists, and active site-binding molecules are currently being developed to reverse the effects of NOACs. The main goal of developing new anticoagulants is to preserve the thromboprophylaxis effect with a low risk of bleeding.

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References / Литература:

1. Lopes L., Spencer F.A., Neumann I. et al. Bleeding risk in atrial fibrillation patients taking vitamin K antagonists: systematic review and meta-analysis. *Clin Pharmacol Ther*. 2013;94(3):367–75. https://doi.org/10.1038/clpt.2013.99.
2. Chai-Adisaksopha C., Crowther M., Isayama T., Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood*. 2014;124(15):2450–8. https://doi.org/10.1182/blood-2014-07-590323.
3. Garcia D.A., Baglin T.P., Weitz J.I., Samama M.M. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e24S–e43S. https://doi.org/10.1378/chest.11-2291.
4. Büller H.R., Davidson B.L., Decousus H. et al. Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: a randomized trial. *Ann Intern Med*. 2004;140(11):867–73. https://doi.org/10.7326/0003-4819-140-11-200406010-00007.
5. Beyer-Westendorf J., Michalski F., Tittl L. et al. Management and outcomes of vaginal bleeding and heavy menstrual bleeding in women of reproductive age on direct oral anti-factor Xa inhibitor therapy: a case series. *Lancet Haematol*. 2016;3(10):e480–e488. https://doi.org/10.1016/S2352-3026(16)30111-9.
6. Gong I.Y., Schwarz U.I., Crown N. et al. Clinical and genetic determinants of warfarin pharmacokinetics and pharmacodynamics during treatment initiation. *PloS One*. 2011;6(11):e27808. https://doi.org/10.1371/journal.pone.0027808.
7. Pirmohamed M., Burnside G., Eriksson N. et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med*. 2013;369(24):2294–303. https://doi.org/10.1056/NEJMoa1311386.
8. Hirsh J., Anand S.S., Halperin J.L., Fuster V. Guide to anticoagulant therapy: Heparin: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;103(24):2994–3018. https://doi.org/10.1161/01.cir.103.24.2994.
9. Olsson S.B., Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362(9397):1691–8. https://doi.org/10.1016/s0140-6736(03)14841-6.
10. Stangier J., Rathgen K., Stähle H. et al. The pharmacokinetics, pharmacodynamics and tolerability of dabigatran etexilate, a new oral direct thrombin inhibitor, in healthy male subjects. *Br J Clin Pharmacol*. 2007;64(3):292–303. https://doi.org/10.1111/j.1365-2125.2007.02899.x.
11. Eriksson B.I., Dahl O.E., Huo M.H. et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). *Thromb Haemost*. 2011;105(4):721–9. https://doi.org/10.1160/TH10-10-0679.
12. Eriksson B., Dahl O., Rosencher N. et al. Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 2007;5(11):2178–85. https://doi.org/10.1111/j.1538-7836.2007.02748.x.
13. Schulman S., Kearon C., Kakkar A.K. et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361(24):2342–52. https://doi.org/10.1056/NEJMoa0906598.
14. Schulman S., Kearon C., Kakkar A.K. et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368(8):709–18. https://doi.org/10.1056/NEJMoa1113697.
15. Connolly S.J., Ezekowitz M.D., Yusuf S. et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–51. https://doi.org/10.1056/NEJMoa0905561.
16. Samama M.M. The mechanism of action of rivaroxaban – an oral, direct Factor Xa inhibitor – compared with other anticoagulants. *Thromb Res*. 2011;127(6):497–504. https://doi.org/10.1016/j.thromres.2010.09.008.
17. Kakkar A.K., Brenner B., Dahl O.E. et al. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. *Lancet*. 2008;372(9632):31–9. https://doi.org/10.1016/S0140-6736(08)60880-6.

18. Patel M.R., Mahaffey K.W., Garg J. et al. Rivaroxaban versus warfarin in nonvalvular Atrial fibrillation. *N Engl J Med*. 2011;365(10):883–91. https://doi.org/10.1056/NEJMoa1009638.
19. Lassen M.R., Raskob G.E., Gallus A. et al. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807–15. https://doi.org/10.1016/S0140-6736(09)62125-5..
20. Lassen M.R., Gallus A., Raskob G.E. et al. Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. *N Engl J Med*. 2010;363(26):2487–98. https://doi.org/10.1056/NEJMoa1006885.
21. Granger C.B., Alexander J.H., McMurray J.J. et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–92. https://doi.org/10.1056/NEJMoa1107039.
22. Agnelli G., Buller H.R., Cohen A. et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369(9):799–808. https://doi.org/10.1056/NEJMoa1302507.
23. Hokusai-VTE Investigators; Büller H.R., Décousus H., Grosso M.A. et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369(15):1406–15. https://doi.org/10.1056/NEJMoa1306638.
24. Giugliano R.P., Ruff C.T., Braunwald E. et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093–104. https://doi.org/10.1056/NEJMoa1310907.
25. Weitz J.I., Chan N.C. Advances in antithrombotic therapy. *Arterioscler Thromb Vasc Biol*. 2019;39(1):7–12. https://doi.org/10.1161/ATVBAHA.118.310960.
26. Pirlog A.-M., Pirlog C.D., Maghiar M.A. DOACs vs vitamin K antagonists: a comparison of phase III clinical trials and a prescriber support tool. *Open Access Maced J Med Sci*. 2019;7(7):1226–32. https://doi.org/10.3889/oamjms.2019.289.
27. Hellenbart E.L., Faulkenberg K.D., Finks S.W. Evaluation of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Manag*. 2017;13:325–42. https://doi.org/10.2147/VHRM.S121661.
28. Wheeler A.P., Gailani D. Why factor XI deficiency is a clinical concern. *Expert Rev Hematol*. 2016;9(7):629–37. https://doi.org/10.1080/17474086.2016.1191944.
29. Gomez K., Bolton-Maggs P. Factor XI deficiency. *Haemophilia*. 2008;14(6):1183–9. https://doi.org/10.1111/j.1365-2516.2008.01667.x.
30. Preis M., Hirsch J., Kotler A. et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood*. 2017;129(9):1210–5. https://doi.org/10.1182/blood-2016-09-742262.
31. Georgi B., Mielke J., Chaffin M. et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. *Stroke*. 2019;50(11):3004–12. https://doi.org/10.1161/STROKEAHA.119.026545.
32. Mavromanoli A.C., Barco S., Konstantinides S.V. Antithrombotics and new interventions for venous thromboembolism: Exploring possibilities beyond factor IIa and factor Xa inhibition. *Res Pract Thromb Haemost*. 2021;5(4):10.1002/rth2.12509. https://doi.org/10.1002/rth2.12509.
33. Yau J.W., Liao P., Fredenburgh J.C. et al. Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. *Blood*. 2014;123(13):2102–7. https://doi.org/10.1182/blood-2013-12-540872.
34. Crosby J.R., Marzec U., Revenko A.S. et al. Antithrombotic effect of antisense factor XI oligonucleotide treatment in primates. *Arterioscler Thromb Vasc Biol*. 2013;33(7):1670–8. https://doi.org/10.1161/ATVBAHA.113.301282.
35. Büller H.R., Bethune C., Bhanot S. et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372(3):232–40. https://doi.org/10.1056/NEJMoa1405760.
36. Eikelboom J., Floege J., Thadhani R. et al. Anticoagulation in patients with kidney failure on dialysis: factor XI as a therapeutic target. *Kidney Int*. 2021;100(6):1199–207. https://doi.org/10.1016/j.kint.2021.08.028.
37. Verhamme P., Yi B.A., Segers A. et al. Abelacimab for prevention of venous thromboembolism. *N Engl J Med*. 2021;385(7):609–17. https://doi.org/10.1056/NEJMoa2105872.
38. Weitz J.I., Bauersachs R., Becker B. et al. Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty: the FOXTROT randomized clinical trial. *JAMA*. 2020;323(2):130–9. https://doi.org/10.1001/jama.2019.20687.
39. Eikelboom J.W., Connolly S.J., Brueckmann M. et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369(13):1206–14. https://doi.org/10.1056/NEJMoa1300615.
40. Jaffer I.H., Stafford A.R., Fredenburgh J.C. et al. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. *J Am Heart Assoc*. 2015;4(8):e002322. https://doi.org/10.1161/JAHA.115.002322.
41. Bethune C., Walsh M., Jung B. et al. Pharmacokinetics and pharmacodynamics of Ionis-FXIRx, an antisense inhibitor of factor XI, in patients with end-stage renal disease on hemodialysis. *Blood*. 2017;130(Suppl 1):1116. https://doi.org/10.1182/BLOOD.V130.SUPPL_1.1116.1116.
42. Kearon C., Akl E.A., Ornelas J. et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–52. https://doi.org/10.1016/j.chest.2015.11.026.
43. Tripodi A. D-dimer testing in laboratory practice. *Clin Chem*. 2011;57(9):1256–62. https://doi.org/10.1373/clinchem.2011.166249.
44. Palareti G., Cosmi B., Legnani C. et al. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med*. 2006;355(17):1780–9. https://doi.org/10.1056/NEJMoa054444.
45. Douketis J., Tosetto A., Marcucci M. et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med*. 2010;153(8):523–31. https://doi.org/10.7326/0003-4819-153-8-201010190-00009.
46. Palareti G., Cosmi B., Legnani C. et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. *Blood*. 2014;124(2):196–203. https://doi.org/10.1182/blood-2014-01-548065.
47. Rodger M.A., Kahn S.R., Wells P.S. et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ*. 2008;179(5):417–26. https://doi.org/10.1503/cmaj.080493.
48. Douxfils J., Gosselin R.C. Laboratory assessment of direct oral anticoagulants. *Semin Thromb Hemost*. 2017;43(3):277–90. https://doi.org/10.1055/s-0036-1597296.
49. Schulman S., Kearon C., Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692–4. https://doi.org/10.1111/j.1538-7836.2005.01204.x.
50. Kaatz S., Ahmad D., Spyropoulos A., Schulman S., Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost*. 2015;13(11):2119–26. https://doi.org/10.1111/jth.13140.
51. Douketis J.D., Arneklev K., Goldhaber S.Z. et al. Comparison of bleeding in patients with nonvalvular atrial fibrillation treated with ximelagatran or warfarin: assessment of incidence, case-fatality rate, time course and sites of bleeding, and risk factors for bleeding. *Arch Intern Med*. 2006;166(8):853–9. https://doi.org/10.1001/archinte.166.8.853.
52. Schulman S., Beyth R.J., Kearon C., Levine M.N. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6):257S–298S. https://doi.org/10.1378/chest.08-0674.
53. Crowther M., Lim W. Low molecular weight heparin and bleeding in patients with chronic renal failure. *Curr Opin Pulm Med*. 2007;13(5):409–13. https://doi.org/10.1097/MCP.0b013e328216430d.
54. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators; Yusuf S., Mehta S.R., Chrolavicius S. et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354(14):1464–76. https://doi.org/10.1056/NEJMoa055443.
55. Yusuf S., Mehta S.R., Chrolavicius S. et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295(13):1519–30. https://doi.org/10.1001/jama.295.13.joc60038.
56. Turpie A.G., Bauer K.A., Eriksson B.I., Lassen M.R. Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopedic surgery: a meta-analysis of 4 randomized double-blind studies. *Arch Intern Med*. 2002;162(16):1833–40. https://doi.org/10.1001/archinte.162.16.1833.

57. Reilly P.A., Lehr T., Haertter S. et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *J Am Coll Cardiol*. 2014;63(4):321–8. https://doi.org/10.1016/j.jacc.2013.07.104.
58. Connolly S.J., Wallentin L., Ezekowitz M.D. et al. The long-term multicenter observational study of dabigatran treatment in patients with atrial fibrillation (RELY-ABLE) study. *Circulation*. 2013;128(3):237–43. https://doi.org/10.1161/CIRCULATIONAHA.112.001139.
59. Dans A.L., Connolly S.J., Wallentin L. et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127(5):634–40. https://doi.org/10.1161/CIRCULATIONAHA.112.115386.
60. Halperin J.L., Halperin JL, Wojdyla D. et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in 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). *Circulation*. 2014;130(2):138–46. https://doi.org/10.1161/CIRCULATIONAHA.113.005008.
61. Crowther M.A., Douketis J.D., Schnurr T. et al. Oral vitamin K lowers the international normalized ratio more rapidly than subcutaneous vitamin K in the treatment of warfarin-associated coagulopathy: a randomized, controlled trial. *Ann Intern Med*. 2002;137(4):251–4. https://doi.org/10.7326/0003-4819-137-4-200208200-00009.
62. DeZee K.J., Shimeall W.T., Douglas K.M. et al. Treatment of excessive anticoagulation with phytonadione (vitamin K): a meta-analysis. *Arch Intern Med*. 2006;166(4):391–7. https://doi.org/10.1001/.391.
63. Watson H.G., Baglin T., Laidlaw S.L. et al. A comparison of the efficacy and rate of response to oral and intravenous Vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol*. 2001;115(1):145–9. https://doi.org/10.1046/j.1365-2141.2001.03070.x.
64. Holbrook A., Schulman S., Witt D.M. et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e152S–e184S. https://doi.org/10.1378/chest.11-2295.
65. Makris M., Greaves M., Phillips W.S. et al. Emergency oral anticoagulant reversal: the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost*. 1997;77(3):477–80.
66. Holland .L, Warkentin T.E., Refaai M. et al. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. *Transfusion*. 2009;49(6):1171–7. https://doi.org/10.1111/j.1537-2995.2008.02080.x.
67. Dentali F., Marchesi C., Pierfranceschi M.G. et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost*. 2011;106(3):429–38. https://doi.org/10.1160/TH11-01-0052.
68. Nishijima D.K., Dager W.E., Schrot R.J., Holmes J.F. The efficacy of factor VIIa in emergency department patients with warfarin use and traumatic intracranial hemorrhage. *Acad Emerg Med*. 2010;17(3):244–51. https://doi.org/10.1111/j.1553-2712.2010.00666.x.
69. Pinner N.A., Hurdle A.C., Oliphant C. et al. Treatment of warfarin-related intracranial hemorrhage: a comparison of prothrombin complex concentrate and recombinant activated factor VII. *World Neurosurg*. 2010;74(6):631–5. https://doi.org/10.1016/j.wneu.2010.06.030.
70. Levi M., Levy J.H., Andersen H.F., Truloff D. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med*. 2010;363(19):1791–800. https://doi.org/10.1056/NEJMoa1006221.
71. Wójcik C., Schymik M.L., Cure E.G. Activated prothrombin complex concentrate factor VIII inhibitor bypassing activity (FEIBA) for the reversal of warfarin-induced coagulopathy. *Int J Emerg Med*. 2009;2(4):217–25. https://doi.org/10.1007/s12245-009-0125-8.
72. Pai M., Crowther M.A. Neutralization of heparin activity. *Handb Exp Pharmacol*. 2012;(207):265-77. https://doi.org/10.1007/978-3-642-23056-1_11.
73. van Veen J.J., Maclean R.M., Hampton K.K. et al. Protamine reversal of low molecular weight heparin: clinically effective? *Blood Coagul Fibrinolysis*. 2011;22(7):565–70. https://doi.org/10.1097/MBC.0b013e3283494b3c.
74. Nybo M., Madsen J.S. Serious anaphylactic reactions due to protamine sulfate: a systematic literature review. *Basic Clin Pharmacol Toxicol*. 2008;103(2):192–6. https://doi.org/10.1111/j.1742-7843.2008.00274.x.
75. Horrow J.C. Protamine: a review of its toxicity. *Anesth Analg*. 1985;64(3):348–61.
76. Bakchoul T., Zöllner H., Amiral J. et al. Anti-protamine-heparin antibodies: incidence, clinical relevance, and pathogenesis. *Blood*. 2013;121(15):2821–7. https://doi.org/10.1182/blood-2012-10-460691.
77. Longstaff C., Hogwood J., Gray E. et al. Neutralization of the anti-coagulant effects of heparin by histones in blood plasma and purified systems. *Thromb Haemost*. 2016;115(3):591–9. https://doi.org/10.1160/TH15-03-0214.
78. Chan S., Kong M., Minning D. et al. Assessment of recombinant factor VIIa as an antidote for bleeding induced in the rabbit by low molecular weight heparin. *J Thromb Haemost*. 2003;1(4):760–5. https://doi.org/10.1046/j.1538-7836.2003.00101.x.
79. Lauritzen B., Hedner U., Johansen P. et al. Recombinant human factor VIIa and a factor VIIa-analogue reduces heparin and low molecular weight heparin (LMWH)-induced bleeding in rats. *J Thromb Haemost*. 2008;6(5):804–11. https://doi.org/10.1111/j.1538-7836.2008.02933.x.
80. Bijsterveld N.R., Moons A.H., Boekholdt S.M. et al. Ability of recombinant factor VIIa to reverse the anticoagulant effect of the pentasaccharide fondaparinux in healthy volunteers. *Circulation*. 2002;106(20):2550–4. https://doi.org/10.1161/01.cir.0000038501.87442.02.
81. Bijsterveld N.R., Vink R., van Aken B.E. et al. Recombinant factor VIIa reverses the anticoagulant effect of the long-acting pentasaccharide idraparinux in healthy volunteers. *Br J Haematol*. 2004;124(5):653–8. https://doi.org/10.1111/j.1365-2141.2003.04811.x.
82. Firozvi K., Deveras R.A.E., Kessler C.M. Reversal of low-molecular-weight heparin-induced bleeding in patients with pre-existing hypercoagulable states with human recombinant activated factor VII concentrate. *Am J Hematol*. 2006;81(8):582–9. https://doi.org/0.1002/ajh.2065.
83. Nagler M., Haslauer M., Wuillemin W.A. Fondaparinux – data on efficacy and safety in special situations. *Thromb Res*. 2012;129(4):407–17. https://doi.org/10.1016/j.thromres.2011.10.037.
84. Gerotziafas G.T., Depasse F., Chakroun T. et al. Recombinant factor VIIa partially reverses the inhibitory effect of fondaparinux on thrombin generation after tissue factor activation in platelet rich plasma and whole blood. *Thromb Haemost*. 2004;91(3):531–7. https://doi.org/10.1160/TH03-07-0483.
85. Lisman T., Bijsterveld N., Adelmeijer J. et al. Recombinant factor VIIa reverses the in vitro and ex vivo anticoagulant and profibrinolytic effects of fondaparinux. *J Thromb Haemost*. 2003;1(11):2368–73. https://doi.org/10.1046/j.1538-7836.2003.00536.x.
86. Akwaa F., Spyropoulos A.C. Treatment of bleeding complications when using oral anticoagulants for prevention of strokes. *Curr Treat Options Cardiovasc Med*. 2013;15(3):288–98. https://doi.org/10.1007/s11936-013-0238-5.
87. van Ryn J., Stangier J., Haertter S. et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost*. 2010;103(6):1116–27. https://doi.org/10.1160/TH09-11-0758.
88. Stangier J., Rathgen K., Stähle H., Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet*. 2010;49(4):259–68. https://doi.org/10.2165/11318170-000000000-00000.
89. Khadzhynov D., Wagner F., Formella S. et al. Effective elimination of dabigatran by haemodialysis. A phase I single-centre study in patients with end-stage renal disease. *Thromb Haemost*. 2013;109(4):596–605. https://doi.org/10.1160/TH12-08-0573.
90. Zhou W., Schwarting S., Illanes S. et al. Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. *Stroke*. 2011;42(12):3594–9. https://doi.org/10.1161/STROKEAHA.111.624650.
91. Eerenberg E.S., Kamphuisen P.W., Sijpkens M.K. et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573–9. https://doi.org/10.1161/CIRCULATIONAHA.111.029017.

92. Marlu R., Hodaj E., Paris A. et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban. *Thromb Haemost*. 2012;108(2):217–24. https://doi.org/10.1160/TH12-03-0179.
93. Dager W.E., Gosselin R.C., Roberts A.J. Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. *Crit Care Med*. 2013;41(5):e42–6. https://doi.org/10.1097/CCM.0b013e31827caaa3.
94. Schulman S., Ritchie B., Goy J.K. et al. Activated prothrombin complex concentrate for dabigatran-associated bleeding. *Br J Haematol*. 2014;164(2):308–10. https://doi.org/10.1111/bjh.12620.
95. van Ryn J., Schurer J., Kink-Eiband M., Clemens A. The successful reversal of dabigatran-induced bleeding by coagulation factor concentrates in a rat tail bleeding model do not correlate with ex vivo markers of anticoagulation. *Blood*. 2011;118(21):2316. https://doi.org/10.1182/blood.V118.21.2316.2316.
96. Pollack C.V., Reilly P.A., van Ryn J. et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med*. 2017;377(5):431–41. https://doi.org/10.1056/NEJMoa1707278.
97. Zhang D., Frost C.E., He K. et al. Investigating the enteroenteric recirculation of apixaban, a factor Xa inhibitor: administration of activated charcoal to bile duct-cannulated rats and dogs receiving an intravenous dose and use of drug transporter knockout rats. *Drug Metab Dispos*. 2013;41(4):906–15. https://doi.org/10.1124/dmd.112.050575.
98. Godier A., Miclot A., Le Bonniec B. et al. Evaluation of prothrombin complex concentrate and recombinant activated factor VII to reverse rivaroxaban in a rabbit model. *Anesthesiology*. 2012;116(1):94–102. https://doi.org/10.1097/ALN.0b013e318238c036.
99. Fukuda T., Honda Y., Kamisato C. et al. Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents. *Thromb Haemost*. 2012;107(2):253–9. https://doi.org/10.1160/TH11-09-0668.
100. Majeed A., Agren A., Holmström M. et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood*. 2017;130(15):1706–12. https://doi.org/10.1182/blood-2017-05-782060.
101. Schulman S., Gross P.L., Ritchie B. et al. Prothrombin complex concentrate for major bleeding on factor Xa inhibitors: a prospective cohort study. *Thromb Haemosts*. 2018;118(5):842–51. https://doi.org/10.1055/s-0038-1636541.
102. Gruber A., Marzec U.M., Buetehorn U., Hanson S., Perzborn E. Potential of activated prothrombin complex concentrate and activated factor VII to reverse the anticoagulant effects of rivaroxaban in primates. *Blood*. 2008;112(11):3825. https://doi.org/10.1182/blood.V112.11.3825.3825.
103. Lu G., DeGuzman F.R., Hollenbach S.J. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med*. 2013;19(4):446–51. https://doi.org/10.1038/nm.3102.
104. Mark C., Kitt M.M., Vandana M. et al. A phase 2 randomized, double-blind, placebo-controlled trial demonstrating reversal of rivaroxaban-induced anticoagulation in healthy subjects by andexanet alfa (PRT064445), an antidote for FXa inhibitors. *Blood*. 2013;122(21):3636. https://doi.org/10.1182/BLOOD.V122.21.3636.3636.
105. Connolly S.J., Crowther M., Eikelboom J.W. et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2019;380(14):1326–35. https://doi.org/10.1056/NEJMoa1814051.
106. Laulicht B., Bakhru S., Lee C. et al. Small molecule antidote for anticoagulants. *Circulation*. 2012;126(Suppl 1):11395.
107. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395(10241):1927–36. https://doi.org/10.1016/S0140-6736(20)30848-5.
108. Hemphill J.C., Greenberg S.M., Anderson C.S. et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46(7):2032–60. https://doi.org/10.1161/STR.0000000000000069.
109. Lansberg M.G., O'Donnell M.J., Khatri P. et al. Antithrombotic and thrombolytic therapy for ischemic stroke: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 Suppl):e601S–e636S. https://doi.org/10.1378/chest.11-2302.
110. Pennlert J., Overholser R., Asplund K. et al. Optimal timing of anticoagulant treatment after intracerebral hemorrhage in patients with atrial fibrillation. *Stroke*. 2017;48(2):314–20. https://doi.org/10.1161/STROKEAHA.116.014643.
111. Nielsen P.B., Larsen T.B., Skjøth F., Lip G.Y. Outcomes associated with resuming warfarin treatment after hemorrhagic stroke or traumatic intracranial hemorrhage in patients with atrial fibrillation. *JAMA Intern Med*. 2017;177(4):563–70. https://doi.org/10.1001/jamainternmed.2016.9369.
112. Gralnek I.M., Dumonceau J.-M., Kuipers E.J. et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47(10):a1–a46. https://doi.org/10.1055/s-0034-1393172.
113. Majeed A., Wallvik N., Eriksson J. et al. Optimal timing of vitamin K antagonist resumption after upper gastrointestinal bleeding. *Thromb Haemost*. 2017;117(3):491–9. https://doi.org/10.1160/TH16-07-0498.

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