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Anticoagulants - The Past, The Present, The Future – A Systematic Review

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Key words: anticoagulant drugs, factor XI inhibitors, coagulation

ABSTRACT

Introduction: Anticoagulants have been discovered and developed over past 100 years. At the beginning unfractionated heparin found its applications, just later to fade into the background of newer and more effective drugs. Patients have been treated with more and more progressive medications – Low-Molecule-Weight Heparin (LMWH), Vitamin K Antagonists (VKA) and Novel Oral Anticoagulants (NOAC). All of them have many indications but most importantly they are used in prophylaxis and treatment of venous thromboembolism (VTE). Scientists and physicians have been working for years to come up with the perfect drug that has fewer contraindications, side effects and doesn't need continuous anticoagulant monitoring. As for today, deemed a turning point in anticoagulant therapy are inhibitors of factor XI. It is a ground-breaking innovation as it ensures high prevention of thrombotic episodes and guarantees intact physiological hemostasis.

Current State of Knowledge: The coagulation cascade and molecules part taking in that have been discovered and described extensively and in detail. Historically, the demand for anticoagulants was always a burning subject. A huge progress has been made in the last one hundred years. Treatment which clinicians are using currently is a combination of drugs used in the past and the novel forms. Unfractionated heparin is the oldest out of all and despite its simple action mechanism and adverse effects, is still a requested drug. Its lighter form, low-molecule-weight-heparin (LMWH) is an enhancement to the previous treatment due to its higher bioavailability and fewer side effects. Vitamin K antagonists (VKAs) are widely

spread in medical environment thanks to their expanded mechanism of action, oral administration and reversibility of their overdose, as well as their well-developed anti-side effect therapy. Novel Oral Anticoagulants (NOACs) have been introduced to the market about 10 years ago. In spite of NOACs short period of clinical use, they were a huge change to the previous treating methods. No need of constant checking the coagulation times was a great convenience to both patients and doctors. Currently, the newest innovation in anticoagulant therapy are inhibitors of factor XI. Even though it still undergoes clinical trials, the outcome is promising for the future.

Summary: The present article discusses history of anticoagulant drugs, their mechanism of action and usage but also focuses on the recent perspectives and developments as new anticoagulant drugs are being put to the test in therapeutic trials. The review underlines the importance and a big demand for improvements in old therapeutic methods and exploring the new, more suitable ones.

Key words: anticoagulant drugs, factor XI inhibitors, coagulation

1. INTRODUCTION

Blood running under pressure in the vessels of circulatory system is a liquid consisting of cells and set of proteins dissolved in plasma. If a vascular failure befalls and blood starts emerging outside of the vasculature, the soluble proteins are triggered and activate in a downstream of coagulation, creating a thrombus (1).

Anticoagulants are drugs that prevent blood from clotting. They are mainly used is in venous thromboembolism (VTE), where they prevent vascular occlusion and its clinical manifestations (2). Thrombosis is one of the main causes of death around the world, and the most common cause in non-contagious diseases (2). Almost 10 million people suffer from VTE each year caused by surgeries, cancer and other risk factors but majority of thromboembolisms is unprompted (3). Other leading VTE vectors are fractures, immobilization, chronic conditions as hypertension, diabetes and kidney disease, and those should be treated with preventative methods first (4). That's why discovery and development of anticoagulant drugs stays as a priority. Anticoagulants are not only used to treat thrombosis simultaneously to present events but also in long-term therapy (5). There are three steps in

VTE treatment: initial management, primary treatment and secondary prevention (6). Initial stabilization aims to annihilate quickly any blood clot from forming by usage of anticoagulant drugs, e.g. unfractionated heparin. Primary treatment lasts from 3 to 6 months past VTE as there is a high risk of recurrence. Final step is the secondary prevention where direct oral anticoagulants (DOACs) find their application (7). Depending on disease being provoked or unprovoked patients are handled with either an indefinite or a finite anticoagulative therapy (6).

Throughout the years many innovations were made in anticoagulants' industry. Various drugs were put on the market and proved to be useful. Other, that didn't pass the test due to their adverse effects and many contraindications, were withdrawn. In this article we would like to present different aspects of anticoagulant drugs' use, their history of introduction to patients' daily life and prospects of what the future discoveries may hold.

2. COAGULATION CASCADE

The theory of blood coagulation cascade, also called "waterfall", was first described by Gwyn Macfarlane, Earl Davie and Oscar Runoff in 1960s. They noticed the main rule of the cascade, which is role of proenzymes starting a course of enzymes activation (8). The "enzyme downstream" is divided into two pathways: extrinsic and intrinsic. Tissue damage is what sets off extrinsic way is initiated with tissue factor exposure. Intrinsic pathway plays its role in blood clogging triggered by contact with artificial materials, e.g. used in MCADs (mechanical circulatory assist device) or cardiopulmonary bypasses (9). Tissue factor, also called factor III, is a glycoprotein anchored in membrane of subendothelial tissues and fibroblast. When vascular derangement or damage occurs, factor III is exposed and attaches to calcium and factor VII. Complex created turns factor X to activated form Xa (10).

Other initiation of factor X to Xa descents from the intrinsic pathway. This sequential model is based on activation of factor XII, then factor XI and further factor IX, called FXIIa, FXIa, FIXa as activated forms. FXIIa, HMW kininogen and prekallikrein generate a conjunction that converts FXI to FXIa. Activated XI catalyzes FIX to FIXa which with its cofactor (factor VIII) combines and transforms factor X to factor Xa (11).

Both, the extrinsic and intrinsic pathways meet simultaneously as FXa binds with calcium, activated factor Va (induced by FII) and accelerates formation of activated factor II, which is called thrombin (12). Complex of FXa causes prothrombin (FII), an unstable plasma protein produced in liver, to disintegrate into smaller parts of which one is factor II [12]. Thrombin is

deemed to be the main effector of blood clotting as it fractures fibrinogen to fibrin and additionally catalyzes factor XIII to initiate clot formation with meshing fibrin (8,9) . The whole process stabilizes thrombus and stops blood leaks and that encourages damaged vessel walls to heal and wound properly(13). On the other hand, if thrombosis happens and the blood flow is disturbed, process which brings back circulation is fibrinolysis. Main proteins that participate in fibrinolysis are plasminogen activators that transform plasminogen to plasmin. Plasmin activates fibrin-net lysis that breaks up the clot formation(14).

Disparities in domination of fibrinolysis or coagulation can manifest as either bleedings or thrombosis. Blockages created by clogged vessels can cause various pathological outcomes: myocardial infraction, ischemic stroke, deep vein thrombosis(13).

3. USE OF ANTICOAGULANTS

An imbalance between anticoagulation and hemostasis mechanism leads to the formation of thrombus. The pathology can occur both in arteries and veins. Arterial thrombosis manifests as an acute stroke, myocardial infarction or acute on the chronic peripheral arterial disease, while venous thromboembolism (VTE) leads to pulmonary embolism (PE) and deep vein thrombosis (DVT)(15).Most of the mentioned diseases remain the leading cause of morbidity and death of patients. the problem which occurred mostly in the high-income countries before, has been increasing all over the world and now has become an international struggle(16). The most important factors predisposing to thromboembolic conditions are smoking, hypertension, obesity, physical inactivity and inadequate diet (17) but also pregnancy and increasing age. Even though the prophylaxis has been constantly improving throughout the years, the number of the venous thrombosis incidents remained stable (18). In the paragraphs below the authors focused on the most common usage of anticoagulants in both healthy and suffering from an illness people. The main interest was given to the air travelers, patients after surgical procedures or those with atrial fibrillation and pregnant women.

3.1 AIR TRAVELING PATIENTS

Explanation of the significance of anticoagulant treatment is especially important minding that thromboembolic episodes can affect patients who are not primary considered as the group of risk.

For example, air traveling increases the risk of DVT in the group over 50 years of age to 10%, and up to 4,5% in younger (19). The studies have shown that in the group of healthy patients

the compression stocking is not necessary, but it still lowers the risk of complications(20).In the patients with the risk factors such as recent trauma or surgery, varicose vein, history of VTE, active cancer, hormone therapy, obesity or post-partum period, the prophylaxis is necessary, especially if the travel duration is longer than 8 hours(21). Default treatment in this group is the knee-high, 15-30 mmHg by ankle compression stocking and in the patients with very high risk of VTE the use of LMWH is considered(22).

3.2 PATIENTS AFTER SURGICAL PROCEDURES

Considering the group of hospitalized patients the risk of VTE increases due to decreased mobility, blood vessel trauma caused by the surgery and other serious injuries(23). With the help of radiolabeled fibrinogen or venography it was possible to acknowledge that almost 30% of patients who went through general surgery had DVT(24). According to the trials more than two-thirds of hospital-acquired thrombosis (HAT), which stands for a new episode of VTE during the hospital stay or 90 days of discharge, are avoidable if the thromboprophylaxis is initiated(25). The preferred anticoagulant treatment in surgical patient is low-molecular-weight heparin (LMWH). The administration of 5000 U of LMWH subcutaneously every 8 to 12 hours is efficient to reduce fatal PE, which is an acute postsurgical complication, by around 60% in patients at risk of VTE(26).

3.3 PATIENTS WITH ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common arrythmia, impacting over 33 million people around the globe, with the numbers still growing(27). The hypercoagulation state in AF can be explained by the Virchow's triad. The set of three combined factors - hypercoagulability, structural abnormalities and blood stasis(28).The risk of ischemic stroke due to AF is three to five times higher in comparison to the rest of the population (29) . For that reason, antithrombotic treatment is especially important. It has been proven that the use of vitamin K antagonists (VKAs) lowers that risk for 66%. According to CHEST guideline novel oral anticoagulation (NOACs) is superior to VKAs, the pros of using NOACs over VKAs are shortly presented below (30) Patients assigned to 110mg of dabigatran twice daily show significantly lower rates of major bleeding compared to warfarin(31) .

However the choice of anticoagulant treatment in patients with AF should be based on physical examination and scales CHAD2DS2-VASc and HAS-BLED as well as the presence

of valvular heart disease, all of those are widely described in the guidelines mentioned above (30).

3.4 PREGNANCY

1 to 2 per 1,000 pregnant women are affected by venous thromboembolism (32). 80% of VTE is manifesting as DVT and 20% as PE. The risk increases from the beginning of pregnancy with its peak in the postpartum period and completely resolves 12 weeks after birth(32).

According to Royal College of Obstetricians and Gynaecologists (RCOG) episode of VTE is more likely in patients with risk factors such as previous VTE or thrombophilia, BMI index >30, age over 35, strict rest longer than 1 week combined with BMI >25, hospitalization during the pregnancy longer than 3 days, smoking or pre-existing diabetes. More thorough explications can be found in the RCOG guidelines (33) . Not crossing the placenta by heparin makes it a fetus safe drug. UFH or LMWH are first-choice drugs. LMWH reveals higher bioavailability, more predictable anticoagulant response and lower risk of adverse effects compared to UFH. In mother thrombocytopenia, allergic reactions and loss of the bone density were observed as an effect of heparins use. After caesarean section increased risk of bleeding and wound complications have been observed(34).

4. HISTORY OF ANTICOAGULANTS

Thrombosis is a condition known and studied by physicians since the ancient times, the term of blood clots can be found in the Hippocratic collection and the reports from early 2nd century CE (35) . While the ancients were using the willow bark, full of a glycoside called salicyline, for reducing pain and relieving gastrointestinal symptoms, the antithrombotic effect of it wasn't discovered until the 20th century(36).

Parallelly at Johns Hopkins Medical School, Baltimore, USA, a second-year medical student Jay McLean and a physiologist William Henry Howell were investigating the balance between clotting inhibitors and procoagulants by extracting phosphatides from canine liver and using them to provoke excessive bleeding in experimental animals, that was the beginning of unfractionated heparin (UFH)(37). The medicine was introduced to the market in 1920s and maintained in the use despite its side effects such as fever, nausea and headaches. The work on purifying the substance continued and the first successful administration was established in 1937 and the drug didn't show any sign of adverse effects(38).

Around the same time in 1930s at the University of Wisconsin Karl Paul Link was investigating sudden decease of cattle in the surrounding farms. After a few years of trials, the scientists discovered that the hay fed to the cattle was contaminated with sweet clover and its toxic component – dicumarol. Extraction of the substance emerge to be an effective vitamin K antagonist(39). Warfarin was first registered as a rat poison, but it was approved to humans in 1954 and in 1955 saved President Eisenhower from myocardial infarction(40).

The first scientific interest in lower molecular weight heparins is dating back to 1970s. Dr Edward Johnson cut highly heterogenous heparin into three parts of low, medium and high molecular weight. Although the study was disputable due to the voluntary participants and insufficient laboratory conditions, the outcome was promising (41). The blood results of the volunteers who received LWMH showed high level of the anti-Xa assay, a marker of the level of functional heparin in the plasma(42).

In the early 2000s, ximelgatran – the first oral direct thrombin inhibitor made its attempt to replace VKAs. The new anticoagulants were supposed to reduce the problems of the old drugs – the need of regular coagulation monitoring and managing the patients with INR fluctuations or drug to drug interactions (43) . The new drugs had attributes such as wide therapeutic window, no INR control required, and fewer dietary interactions, what was an encouragement to continue the research (44) . Even though ximelgatran was eventually withdrawn from the market due to its hepatotoxicity, the studies carried on (45) . In 2010 the first FDA-approved direct oral anticoagulant (DOAC) – dabigatran, was discovered and a new window of opportunity has been opened(46). In the following years rivaroxaban, apixaban and edoxaban were introduced to the market.

5. UNFRACTIONATED HEPARIN

Unfractionated heparin (UFH) is a sulphated polysaccharide that weights from 3000 to 30 000 Da (47) . Even though it got discovered over one hundred years ago, it is still widely used in the treatment and prevention of thrombotic events (48,49) . The application of UFH is controversial, because despite its advantages, there are risks posed by its use. Dosing of the drug is highly difficult and maintaining its therapeutic effect is also a challenge. As studies have shown about 5.5% of patients treated with excessive dose of UFH experience bleeding (50) . To optimize the portions, clinicians diligently measure maintenance doses and boluses with weight-based formulas. For bolus it is established by dividing units of UFH by kilograms and for maintenance doses UFH kg/hour (50).

Heparin's anticoagulant effect is caused by cohering to antithrombin (AT) and interfering in the coagulation cascade by blocking factor IIa (thrombin) and factor Xa. The molecule has a pentasaccharide present on its surface, which has high affinity to antithrombin. When UFH and AT bind, that leads to thrombin inactivation. Fibrinogen cannot be transformed to fibrin and clotting time of blood gets prolonged(51)**.**

Main disadvantage of UFH and its mechanism of action is that it binds to an array of different positively charged proteins. Heparin can attach not only to AT, but plasma proteins, platelets' proteins or endothelial cells and that manifests as diverse anticoagulant response(47). Another limitation of heparin is induced thrombocytopenia (HIT) and osteopenia. About 5% of patients using heparin suffer from HIT. It has been shown that UFH is more likely to induce thrombocytopenia than any other anticoagulant (52). Due to the various responses in patients, activated partial thromboplastin time (APTT) must be tracked. APTT therapeutic range varies, and the ratio accepted among patients is an increase of 1,5 – 2,5 times the output value(53).

Unfractionated heparin may be administered in two ways, either by intravenous injection or subcutaneous one. Effects based on the method of administration differ as IV is applied in constant therapeutic anticoagulation, and prevention of thromboembolism is mainly achieved by subcutaneous route(51).

UFH is a widely used drug in prophylaxis and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). On the other hand, it finds its application in dialysis – when acute kidney injury occurs, cardiac surgeries- coronary angioplasty, extracorporeal circulation and in atrial fibrillation as an alternative to oral anticoagulants(47,51).

6. LOW-MOLECULAR- WEIGHT HEPARINS (LMWH)

Heparins, e.g. dalteparin, enoxaparin, are glycoaminoglycans which are built of chains with alternating residues of D-glucosamines and uronic acid. LMWH's chains mean weight states as 5 000 Da. In comparison to heparin, which chains consist of at the minimum 18 saccharide units, less than half of LMWH chains are this long. Due to this, heparin attaches to antithrombin (AT) and thrombin, whereas low-weight molecules (LMWH) don't do it and bind to AT and factor Xa stronger and more effectively. This conjunction inactivates factor Xa(54).

Low-molecular-weight heparins have higher bioavailability than UFH because of their lower binding abilities to plasma proteins. Because of that, demand for coagulation level monitoring is not as high as with unfractionated heparin (55) . Other advantages over UFH are fewer

events of heparin-induced thrombocytopenia (HIT) and osteopenia, but also LMWH dosing is less complicated as clinicians can foresee a response among patients to certain dose of the drug (47) . LMWH established dose is administered subcutaneously and as there is no compulsory need for continuous anticoagulant monitoring, patients can be discharged from a hospital and treated from home(2).

At the end of July 2010 Food and Drug Administration (FDA) approved first LMWH for clinical use. These drugs found their application first in prevention and treatment of venous thromboembolic disease (VTE) (56) . Other purposes of LMWH approved by The British National Formulary (BNF) and National Institute for Health and Care Excellence (NICE) count among: surgical, orthopedic patients suffering from deep vein thromboses, patients with STEMI, unstable angina and those using extracorporeal circulation. Low-molecular-weight heparins can be administered to both pregnant and nonpregnant women(57).

Not only LMHW is an anticoagulant drug but also its novel anti-inflammatory and anti-cancer features were discovered and may serve in the future as new indications. Because the parenteral way of administration is found to be unfavorable to patients, new micro- and nano-systems of drugs' delivery have been worked on and have been improved to enhance its bioavailability and retention time(58).

7. VITAMIN K ANTAGONISTS (VKAs)

VKAs were the mainstay of treatment for the last 50 years. Warfarine, acenokumarol and phenoprocoumon indirectly inactivate factors II, VII, IX, X and proteins C and S(59). Vitamin K transforms into vitamin K hydroquinone (KH_2) via redox conversion cycle, KH_2 drives the γ- carboxylation of a glutamate-rich domain of factors II, VII, IX, X and protein C, Z and S. During the injury the carboxylated domain enables calcium-membrane part of the coagulation factors and their subsequent assemblance starts the coagulation cascade. To regenerate KH_2 the activity of vitamin K epoxide reductase (VKOR) is needed. VKAs inhibit the VKOR and as a results there is no KH_2 to activate the cascade(60).

Oral administration of VKAs is useful in anti-thrombotic prophylaxis of VTE, AF and cardiac mechanical valves, but during the treatment the International Normalized Ratio (INR) must be under constant control (61) . The default INR level in patients treated with VKAs is between 2 and 3, but in the patients with high risk of VTE the desired levels are higher (62) .VKAs are characterized by slow therapeutic onset of action and multiple food, drugs and genetic interactions. In result the pharmacology of VKAs is highly unpredictable,

moreover the therapeutic index is very narrow which results in difficulties with dose adjustments and the need of constant monitoring(63). The risk of bleeding is the highest at the beginning of the treatment. In case of major bleedings VKA reversal strategy needs to be used, a prothrombin complex concentrate infusion and vitamin K until the INR is higher than 1.5(64). VKAs can also cause vascular calcification that leads to cardiovascular disease(65). Regardless of their side effects and the treating difficulties they still are very useful and effective drugs when it comes to thromboembolic conditions.

8. NOVEL ORAL ANTICOAGULANTS (NOACs)

The group of NOACs that are currently in the medical use consists of dabigatran, rivaroxaban, apixaban and edoxaban. Dabigatran is a direct thrombin inhibitor, when rivaroxaban, edoxaban and apixaban inhibit anti-Xa factor. Though the drugs are usually considered as one group, each of them has a unique molecular structure which has been presented in table 1. based on National Center for Biotechnology Information(66).

Table 1. Novel oral anticoagulants – the molecular structure and oral bioavailability.

	Molecular weight [Da]	Biochemical groups of affiliation	Oral bioavailability [%]	Ref.
Dabigatran	471.5	aromatic amide from the benzimidazoles group, carboxamidines, pyridines, derivatives of beta-alanine	7	(66,67)
Rivaroxaban	435.9	thiophenes, an organochlorine compound, oxazolidinones, lactams, aromatic amides, monocarboxylic acid amides	66	(66,67)
Apixaban	548.1	pyrazolopyridines, piperidones, lactams, aromatic ethers	50	(66,67)
Edoxaban	459.5	monocarboxylicacid amides, chloropyridines,	68	(66,67)

		thiazolopyridines		

The use of NOACs is wide and no need of constant INR makes them almost perfect drugs for the patients and for the doctors. VTE prophylaxis following orthopedic surgeries, DVT and PE prevention, stroke prevention in nonvalvular AF, VTE prevention in patients after myocardial infarction or those with coronary arteries disease (63). NOACs are currently the first-choice treatment in elderly patients. In the meta-analysis with 42,411 volunteers, NOACs reduced the risk of stroke or embolic events, hemorrhagic stroke and intercranial hemorrhage respectively for 19%, 51% and 52% in comparison to warfarin. As well the significant reduction of all-cause mortality was observed, unfortunately the risk of gastrointestinal bleeding was higher(68).

The main concern in NOACs was the lack of antidote, low bioavailability effecting in variable plasma concentration and the dependence on renal elimination especially in elderly patients with renal disfunction (69). Considering the patients with chronic kidney disease (CKD) in stages from 1 to 3 the use of NOACs is preferred and in stage 4 - NOACs or warfarin. Although in end-stage renal disease warfarin remains the first line treatment (70). Apixaban, rivaroxaban and edoxaban are not recommended with the creatine clearance (CrCl) <15 ml/min, and dabigatran should not be used when the CrCl <30 ml/min (66). Luckily the fast research progress helped to introduce the antidotes to the market. Idarucizumab for dabigatran and andexanet alfa for the factor Xa inhibitors(59). NOACs are usually well tolerated, and the main adverse effects can be bleeding of different variety from bruising and gum bleeding to major such as blood vomiting or intercranial hemorrhage. Other studies have shown that it can also influence the liver, skin, immunology response and the hair(71).

9. FXIa INHIBITORS

A novel therapeutic approach providing a compromise between bleeding and thrombosis is highly demanded due to the limitations of currently used anticoagulants - available pharmacological antithrombotic prophylaxis involves a small but relevant risk of bleeding. Although the selection of anticoagulants made a tremendous progress in the last century, there is still a need for a new agent. Examined in recent years, factor XI inhibitors (FXI inhibitors) aspire to become the next breakthrough in the anticoagulant history. Factor XI inhibitors can be classified in several groups considering their biological construction and mechanism of action. Small molecule inhibitors (milvexian, asundexian) act through inhibiting FXIa –

factor's XI active form, monoclonal antibodies (abelacimab, osocimab, xisomab) bind either FXI or FXIa, antisense oligonucleotides (FXI-ASO, fesomersen) inhibit the synthesis of FXI (72). There is also a group of natural inhibitors isolated from living organisms – snakes, bats - currently not explored in terms of medical usage (73). Ongoing research on FXI inhibitors focus on its usage in several patient groups: patients undergoing total knee arthroplasty, atrial fibrillation, kidney failure, patients with cancer in need of VTE prophylaxis, mild and moderate liver impairment (74). Data obtained from the studies suggest that FXI inhibitors may act as non-inferior agents in prevention of thromboembolic events in comparison to conventional anticoagulants such as heparin - enoxaparin (75,76)or enoxaparin combined with NOAC - apixaban (77).

FXI inhibitors in patients with total knee arthroplasty and atrial fibrillation were examined in several clinical trials – data summarized below in Table 2, all the information can be found at clinicaltrials.gov.

Table 2. Recent studies of new anticoagulants – factor XI inhibitors compared to currently used agents in prevention of thromboembolism in patients undergoing total knee arthroplasty.

Study identification number	Name of FXI inhibitor	Phase of the trial	Aim of the study	Administration route	Results
NCT03891524	Milvexian	2	Comparing the effects of Milvexian to Enoxaparin	Milvexian: Orally for 10 to 14 postoperative days at doses: 25/50/100/200mg Enoxaparin: 40 mg once daily subcutaneously for 10 to 14 postoperative days	Milvexian proved to be more efficient in preventing venous thromboembolism than enoxaparin
NCT01713361	FXI-ASO	2	Comparing the effects of FXI-ASO to Enoxaparin	FXI-ASO: subcutaneously 7 times prior to surgery, 2 times after the surgery at doses 200/300mg Enoxaparin: once daily 40mg subcutaneously	Reducing FXI level contributed to the prevention of thromboembolism, FXI-ASO was well-tolerated
NCT03276143	Osocimab	2	Comparing Osocimab to Enoxaparin and Apixaban	Osocimab: intravenously 0,3/0,6/1,2/1,8mg/kg Enoxaparin: subcutaneously 40mg Apixaban: orally 2,5mg	Postoperavie injections of Osocimab as dose of 1,8mg/kg was superior to Enoxaparin

FXI inhibitors are expected to supplement the unmet criteria of currently used antithrombotic agents as well as have their own, first-party place within the wide range of therapeutic demand. At present, most coagulants interfere with factors X/Xa or II/IIa which are the key points of the coagulation cascade. They may not only replace most popular DOACs in some patient groups where direct oral anticoagulants were not adequately tested like those with liver malfunctions or severe renal insufficiency (78). Studies showed in Table 2 and Table 3 present some promising evidence that FXI inhibitors may prove efficient in prevention of thrombotic disorders. However, further exploration is needed to fully understand the relevance and possible application of these new agents.

Table 3. Recent studies of new anticoagulants – factor XI inhibitors compared to currently used agents in prevention of thromboembolism in patients with atrial fibrillation.

Study identification number	Name of FXI inhibitor	Phase of the trial	Aim of the study	Administration route	Results
NCT04218266	Asundexian	2	Comparing the effects of Asundexian to Apixaban	Asundexian: Orally once daily at doses 20/50mg NOAC – Apixaban: twice daily 5mg	Asundexian resulted in lower rates of bleeding compared with apixaban
NCT04755283	Abelacimab	2	Comparing the effects of Abelacimab to Rivaroxaban	Abelacimab: once monthly, subcutaneously 150 mg/mL Rivaroxaban: orally once daily at doses 15/20mg	Not provided – study completion date: 2025-01

10. SUMMARY

The antithrombotic therapy has been a challenge since the beginning of medicine. Many years of trial-and-error lead to a modern model of treatment. The variety of currently accessible anticoagulant drugs such as UFH, LMWH, VKAs and NOACs, enables the physicians to treat the thromboembolic diseases effectively, but they still face some difficulties. The increasing age of population results in a growing need of finding even better and more efficient drugs. The elderly patients who are burdened with diseases of affluence will need the best form of treatment with possible low index of bleeding risk, renal disfunction and other organ damages. Luckily the work of the scientists is progressing every year, getting us closer to the best possible forms of curing the diseases.

Author's Contribution:

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References:

1. Smith SA, Travers RJ, Morrissey JH. How it all starts: initiation of the clotting cascade. Crit Rev Biochem Mol Biol [Internet]. 2015 Jul 4 [cited 2024 Mar 17];50(4):326. Available from: /pmc/articles/PMC4826570/
2. Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. Cells [Internet]. 2022 Oct 1 [cited 2024 Mar 13];11(20). Available from: /pmc/articles/PMC9600347/
3. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet [Internet]. 2021 Jul 3 [cited 2024 Mar 16];398(10294):64–77. Available from: https://pubmed.ncbi.nlm.nih.gov/33984268/
4. Risk Factors for Venous Thromboembolism | American Heart Association [Internet]. [cited 2024 Mar 16]. Available from: https://www.heart.org/en/health-topics/venous-thromboembolism/risk-factors-for-venous-thromboembolism-vte
5. Weitz JI, Harenberg J. New developments in anticoagulants: Past, present and future. Thromb Haemost [Internet]. 2017 [cited 2024 Mar 16];117(7):1283–8. Available from: http://www.thieme-connect.com/products/ejournals/html/10.1160/TH16-10-0807
6. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol [Internet]. 2023 Apr 1 [cited 2024 Mar 14];20(4):248. Available from: /pmc/articles/PMC9579604/
7. Renner E, Barnes GD. Antithrombotic Management of Venous Thromboembolism: JACC Focus Seminar. J Am Coll Cardiol [Internet]. 2020 Nov 3 [cited 2024 Mar 17];76(18):2142–54. Available from: https://www.jacc.org/doi/10.1016/j.jacc.2020.07.070
8. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth [Internet]. 2014 Sep 1 [cited 2024 Mar 16];58(5):515. Available from: /pmc/articles/PMC4260295/
9. Achneck HE, Sileshi B, Parikh A, Milano CA, Welsby IJ, Lawson JH. Pathophysiology of bleeding and clotting in the cardiac surgery patient: From vascular endothelium to circulatory assist device surface. Circulation [Internet]. 2010 Nov 16 [cited 2024 Mar 17];122(20):2068–77. Available from: https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.110.936773
10. Umerah C o., Momodu II. Anticoagulation. Cardiology Board Review, Second Edition [Internet]. 2023 Jul 17 [cited 2024 Mar 17];615–26. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560651/

11. Grover SP, Mackman N. Intrinsic Pathway of Coagulation and Thrombosis. Arterioscler Thromb Vasc Biol [Internet]. 2019 Mar 1 [cited 2024 Mar 17];39(3):331–8. Available from: https://www.ahajournals.org/doi/abs/10.1161/ATVBAHA.118.312130
12. Palta S, Saroa R, Palta A. Overview of the coagulation system. Indian J Anaesth [Internet]. 2014 Sep 1 [cited 2024 Mar 17];58(5):515. Available from: /pmc/articles/PMC4260295/
13. Weisel JW, Litvinov RI. Fibrin Formation, Structure and Properties. Subcell Biochem [Internet]. 2017 Jan 1 [cited 2024 Mar 18];82:405. Available from: /pmc/articles/PMC5536120/
14. Risman RA, Kirby NC, Bannish BE, Hudson NE, Tutwiler V. Fibrinolysis: an illustrated review. Res Pract Thromb Haemost [Internet]. 2023 Feb 1 [cited 2024 Mar 18];7(2):100081. Available from: /pmc/articles/PMC10024051/
15. Ashorobi D, Ameer MA, Fernandez R. Thrombosis. Cases in Laboratory Genetics and Genomics (LGG) Practice [Internet]. 2023 Aug 8 [cited 2024 Mar 16];125–8. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430/
16. Franchini M, Liumbruno GM, Bonfanti C, Lippi G. The evolution of anticoagulant therapy. Blood Transfusion [Internet]. 2016 Mar 1 [cited 2024 Mar 14];14(2):175. Available from: /pmc/articles/PMC4781787/
17. Mannucci PM, Franchini M. Old and new anticoagulant drugs: A minireview. Ann Med [Internet]. 2011 Mar [cited 2024 Mar 14];43(2):116–23. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=iann20
18. Mavrakanas T, Bounameaux H. The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. Pharmacol Ther. 2011 Apr 1;130(1):46–58.
19. Bendz B, Sandset PM. Deep-vein thrombosis in long-haul flights. The Lancet. 2001 Sep;358(9284):837–8.
20. Schwarz T, Siegert G, Oettler W, Halbritter K, Beyer J, Frommhold R, et al. Venous Thrombosis After Long-haul Flights. Arch Intern Med [Internet]. 2003 Dec 8 [cited 2024 Mar 17];163(22):2759–64. Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/757492
21. Watson HG, Baglin TP. Guidelines on travel-related venous thrombosis. [cited 2024 Mar 17]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2010.08408.x
22. Philbrick JT, Shumate R, Siadaty MS, Becker DM. Air Travel and Venous Thromboembolism: A Systematic Review. Medicine. 2007;22:107–14.

23. Ambra N, Mohammad OH, Naushad VA, Purayil NK, Mohamedali MG, Elzouki AN, et al. Venous Thromboembolism Among Hospitalized Patients: Incidence and Adequacy of Thromboprophylaxis – A Retrospective Study. Vasc Health Risk Manag [Internet]. 2022 [cited 2024 Mar 17];18:575. Available from: /pmc/articles/PMC9333096/
24. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in Fatal Pulmonary Embolism and Venous Thrombosis by Perioperative Administration of Subcutaneous Heparin. http://dx.doi.org/101056/NEJM198805053181805 [Internet]. 2010 Jan 14 [cited 2024 Mar 16];318(18):1162–73. Available from: https://www.nejm.org/doi/10.1056/NEJM198805053181805
25. Encke A, Haas S, Kopp I. The Prophylaxis of Venous Thromboembolism. Dtsch Arztebl Int [Internet]. 2016 Aug 8 [cited 2024 Mar 14];113(31–32):532. Available from: /pmc/articles/PMC5012163/
26. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of Action and Pharmacology of Unfractionated Heparin. 2001 [cited 2024 Mar 16]; Available from: http://www.atvb.org
27. Wijesurendra RS, Casadei B. Mechanisms of atrial fibrillation. Heart [Internet]. 2019 Dec 1 [cited 2024 Mar 16];105(24):1860–7. Available from: https://pubmed.ncbi.nlm.nih.gov/31444267/
28. Yew Ding W, Protty MB, Davies IG, Lip GY. Relationship between lipoproteins, thrombosis, and atrial fibrillation. [cited 2024 Mar 16]; Available from: https://academic.oup.com/cardiovascres/article/118/3/716/6111888
29. Barra S, Providência R. Anticoagulation in atrial fibrillation. Heart [Internet]. 2021 Mar 1 [cited 2024 Mar 15];107(5):419–27. Available from: https://heart.bmj.com/content/107/5/419
30. Lip GYH, Banerjee ; Amitava, Boriani G, Chern En Chiang ;, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. Chest [Internet]. 2018 [cited 2024 Mar 17];154:1121–201. Available from: https://doi.org/10.1016/j.chest.2018.07.040
31. Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and valvular heart disease. Circulation. 2016 Aug 23;134(8):589–98.
32. Middeldorp S, Naue C, Köhler C. Thrombophilia, Thrombosis and Thromboprophylaxis in Pregnancy: For What and in Whom? Hamostaseologie [Internet]. 2022 [cited 2024 Mar 17];42:54–64. Available from: https://doi.org/

33. Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium Green-top Guideline No. 37a. 2015;
34. MiddletonP GJ. Cochrane Library Cochrane Database of Systematic Reviews Venous thromboembolism prophylaxis for women at risk during pregnancy and the early postnatal period (Review). 2021 [cited 2024 Mar 17]; Available from: www.cochranelibrary.com
35. Montinari MR, Minelli S, De Caterina R. Eighty years of oral anticoagulation: Learning from history. Vascul Pharmacol. 2021 Dec 1;141:106918.
36. Montinari MR, Minelli S, De Caterina R. The first 3500 years of aspirin history from its roots-A concise summary. 2018 [cited 2024 Mar 15]; Available from: www.elsevier.com/locate/vph
37. Wardrop D, Keeling D. The story of the discovery of heparin and warfarin. Br J Haematol. 2008 Jun;141(6):757–63.
38. Singh D. 100 Years of Heparin (1916-2016): Saga of Joys and Tears. Indian Journal of Vascular and Endovascular Surgery [Internet]. 2016 [cited 2024 Mar 15];3(4):128. Available from: https://journals.lww.com/ijvs/fulltext/2016/03040/100_years_of_heparin__1916_2016___saga_of_joys_and.4.aspx
39. Russo V, Imbalzano E, Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, et al. Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. 2022 [cited 2024 Mar 15]; Available from: https://doi.org/10.3390/cells11203214
40. Ramachandran S, Pitchai S. Story of warfarin: From rat poison to lifesaving drug. Indian Journal of Vascular and Endovascular Surgery [Internet]. 2018 [cited 2024 Mar 19];5(3):174. Available from: https://journals.lww.com/ijvs/fulltext/2018/05030/story_of_warfarin__from_rat_poison_to_lifesaving.10.aspx
41. Barrowcliffe TW. History of heparin. Handb Exp Pharmacol [Internet]. 2012 [cited 2024 Mar 15];207:3–22. Available from: https://link.springer.com/chapter/10.1007/978-3-642-23056-1_1
42. Anti-Xa assays: What is their role today in antithrombotic therapy? [cited 2024 Mar 16]; Available from: www.ccjm.org
43. Altiok E, Marx N. Oral anticoagulation—update on anticoagulation with vitamin K antagonists and non– vitamin K–dependent oral anticoagulants. Dtsch Arztebl Int . 2018;(115):776–83.

44. Ansell J. Is there a need for an alternative in the era of novel anticoagulants? Expert Rev Cardiovasc Ther [Internet]. 2015 Sep 2 [cited 2024 Mar 15];13(9):967–70. Available from: https://www.tandfonline.com/action/journalInformation?journalCode=ierk20
45. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. Arterioscler Thromb Vasc Biol [Internet]. 2015 May 27 [cited 2024 Mar 15];35(5):1056–65. Available from: https://pubmed.ncbi.nlm.nih.gov/25792448/
46. Wei S, Sawhney A, Khandait H, Meda A, Gupta V, Jain R. An update on applications and limitations of direct oral anticoagulants. Egypt J Intern Med. 2023 Apr 10;35(1).
47. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of Action and Pharmacology of Unfractionated Heparin. 2001 [cited 2024 Mar 18]; Available from: http://www.atvb.org
48. Dinis da Gama A. [The unknown history of heparin's discovery]. Rev Port Cir Cardiotorac Vasc [Internet]. 2008 Jan 1 [cited 2024 Mar 18];15(1):25–30. Available from: https://europepmc.org/article/med/18618048
49. Derbalah A, Duffull S, Newall F, Moynihan K, Al-Sallami H. Revisiting the Pharmacology of Unfractionated Heparin. Clin Pharmacokinet [Internet]. 2019 Aug 1 [cited 2024 Mar 18];58(8):1015–28. Available from: https://link.springer.com/article/10.1007/s40262-019-00751-7
50. Abdel-Hafez A, Scott IA, Falconer N, Canaris S, Bonilla O, Marxen S, et al. Predicting Therapeutic Response to Unfractionated Heparin Therapy: Machine Learning Approach. Interact J Med Res [Internet]. 2022 Sep 19 [cited 2024 Mar 18];11(2):e34533. Available from: /pmc/articles/PMC9531006/
51. Watkins E, Thomas Ginat D, Small JE. Heparin. Neuroimaging Pharmacopoeia, Second Edition [Internet]. 2023 Jul 10 [cited 2024 Mar 19];313–6. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538247/
52. Nicolas D, Nicolas S, Hodgens A, Reed M. Heparin-Induced Thrombocytopenia. StatPearls [Internet]. 2023 May 16 [cited 2024 Mar 19]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK482330/
53. Arachchillage DRJ, Kamani F, Deplano S, Banya W, Laffan M. Should we abandon the APTT for monitoring unfractionated heparin? Thromb Res. 2017 Sep 1;157:157–61.
54. SHARMA S. LOW MOLECULAR WEIGHT HEPARINS. Med J Armed Forces India [Internet]. 1998 Jul [cited 2024 Mar 19];54(3):285. Available from: /pmc/articles/PMC5531654/

55. Akhtar F, Wan X, Wu G, Kesse S, Wang S, He S. Low-Molecular-Weight Heparins: Reduced Size Particulate Systems for Improved Therapeutic Outcomes. Molecules : A Journal of Synthetic Chemistry and Natural Product Chemistry [Internet]. 2018 [cited 2024 Mar 19];23(7). Available from: /pmc/articles/PMC6100363/
56. Harenberg J. Overview on guidelines and recommendations for generic low-molecular-weight heparins. Thromb Res [Internet]. 2011 Feb [cited 2024 Mar 19];127 Suppl 3(SUPPL. 3). Available from: https://pubmed.ncbi.nlm.nih.gov/21262425/
57. Solari F, Varacallo M. Low-Molecular-Weight Heparin (LMWH). StatPearls [Internet]. 2023 Aug 4 [cited 2024 Mar 19]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK525957/
58. Ibrahim SS, Osman R, Awad GAS, Mortada ND, Geneidy AS. Low molecular weight heparins for current and future uses: approaches for micro- and nano-particulate delivery. Drug Deliv [Internet]. 2016 Oct 12 [cited 2024 Mar 19];23(8):2661–7. Available from: https://www.tandfonline.com/doi/abs/10.3109/10717544.2015.1046570
59. Milling TJ, Ziebell CM. A review of oral anticoagulants, old and new, in major bleeding and the need for urgent surgery R. Trends Cardiovasc Med [Internet]. 2020 [cited 2024 Mar 19];30:86–90. Available from: https://doi.org/10.1016/j.tcm.2019.03.004
60. Liu S, Shen G, Li W. Structural and cellular basis of vitamin K antagonism. 2022;
61. Barcellona D, Fenu L, Marongiu F. Point-of-care testing INR: An overview. Clin Chem Lab Med [Internet]. 2017 Jun 1 [cited 2024 Mar 19];55(6):800–5. Available from: https://www.degruyter.com/document/doi/10.1515/cclm-2016-0381/html
62. Dorgalaleh A, Favaloro EJ, Mehran Bahraini |, Rad | Fariba. Standardization of Prothrombin Time/International Normalized Ratio (PT/INR). Int J Lab Hematol [Internet]. 2021 [cited 2024 Mar 19];43:21–8. Available from: https://onlinelibrary.wiley.com/doi/10.1111/ijlh.13349
63. Salem JE, Sabouret P, Funck-Brentano C, Hulot JS. Pharmacology and mechanisms of action of new oral anticoagulants. [cited 2024 Mar 19]; Available from: https://onlinelibrary.wiley.com/doi/10.1111/fcp.12091
64. Lapostolle F, Siguret V, Martin AC, Pailleret C, Vigué B, Zerbib Y, et al. Vitamin K antagonists and emergencies. Eur J Emerg Med [Internet]. 2018 Dec 1 [cited 2024 Mar 19];25(6):378–86. Available from: https://pubmed.ncbi.nlm.nih.gov/29462053/

65. Van Gorp RH, Schurgers LJ. New Insights into the Pros and Cons of the Clinical Use of Vitamin K Antagonists (VKAs) Versus Direct Oral Anticoagulants (DOACs). 2015 [cited 2024 Mar 19]; Available from: www.mdpi.com/journal/nutrients
66. Saviano A, Brigida M, Petruzziello C, Candelli M, Gabrielli M, Ojetti V. Gastrointestinal Bleeding Due to NOACs Use: Exploring the Molecular Mechanisms. 2022 [cited 2024 Mar 19]; Available from: https://doi.org/10.3390/ijms232213955
67. Wojtowicz D, Tomaszuk-Kazberuk A, Małyszko J, Koziński M. HEMATURIA AND OTHER KINDS OF BLEEDINGS ON NON-VITAMIN K ANTAGONIST ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION: AN UPDATED OVERVIEW ON OCCURRENCE, PATHOMECHANISMS AND MANAGEMENT. Wiad Lek. 2020;73(11):2528–34.
68. Ruff CT, Giugliano RP, Braunwald E, Hoff EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the effi cacy and safety of new oral anticoagulants with warfarin in patients with atrial fi brillation: a meta-analysis of randomised trials. www.thelancet.com [Internet]. 2014 [cited 2024 Mar 19];383. Available from: http://dx.doi.org/10.1016/
69. Malmström RE, Godman BB, Diogene E, Baumgärtel C, Bennie M, Bishop I, et al. Dabigatran – a case history demonstrating the need for comprehensive approaches to optimize the use of new drugs. Iñaki Gutiérrez-Ibarluzea [Internet]. [cited 2024 Mar 19];12. Available from: www.frontiersin.org
70. Singh Paresh Pai Harish Kumar Sheeba George Sandeep Mahapatra Vineet Garg N Gupta Kiran Makineni Gaurav Ganeshwala Pravin Narkhede Syed M H Naqvi Kumar Gaurav Mohammed Y K Hukkeri BG, Singh B, Pai P, Kumar H, George S, Mahapatra S, et al. Expert Recommendations on the Usage of Non-vitamin K Antagonist Oral Anticoagulants (NOACs) from India: Current Perspective and Future Direction. 2022 [cited 2024 Mar 19];11:49–79. Available from: https://doi.org/10.1007/s40119-022-00254-w
71. Christopoulou EC, Filippatos TD, Elisaf MS. Non-hemorrhage-related adverse effects of rivaroxaban. Archives of Medical Science – Atherosclerotic Diseases. 2017 Dec 31;2(1):108–12.
72. Nopp S, Kraemmer D, Ay C. Factor XI Inhibitors for Prevention and Treatment of Venous Thromboembolism: A Review on the Rationale and Update on Current Evidence. Vol. 9, Frontiers in Cardiovascular Medicine. 2022.
73. Musiał J. Factor XI inhibitors — a breakthrough in prevention and treatment of thromboembolic disorders. Journal of Transfusion Medicine. 2022;15(4).

74. Perera V, Abelian G, Li D, Wang Z, Zhang L, Lubin S, et al. Single-Dose Pharmacokinetics of Milvexian in Participants with Mild or Moderate Hepatic Impairment Compared with Healthy Participants. Clin Pharmacokinet. 2022;61(6).
75. Weitz JI, Strony J, Ageno W, Gailani D, Hylek EM, Lassen MR, et al. Milvexian for the Prevention of Venous Thromboembolism. New England Journal of Medicine. 2021;385(23).
76. Büller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, et al. Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis. New England Journal of Medicine. 2015;372(3).
77. Weitz JI, Bauersachs R, Becker B, Berkowitz SD, Freitas MCS, Lassen MR, et al. Effect of Osocimab in Preventing Venous Thromboembolism among Patients Undergoing Knee Arthroplasty: The FOXTROT Randomized Clinical Trial. JAMA - Journal of the American Medical Association. 2020;323(2).
78. Muscente F, De Caterina R. The new in anticoagulation: factor XI inhibitors. European Heart Journal Supplements. 2023;25(Supplement_B).