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REVIEW

Drugs in phase I and II clinical development for the prevention of stroke in patients with atrial fibrillation

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ABSTRACT

Introduction: Atrial fibrillation is the most frequently diagnosed cardiac arrhythmia globally and is associated with ischemic stroke and heart failure. Patients with atrial fibrillation are typically prescribed long-term anticoagulants in the form of either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants; however, both carry a potential risk of adverse bleeding.

Areas Covered: This paper sheds light on emerging anticoagulant agents which target clotting factors XI and XII, or their activated forms – XIa and XIIa, respectively, within the intrinsic coagulation pathway. The authors examined data available on PubMed, Scopus, and the clinical trials registry of the United States National Library of Medicine (www.clinicaltrials.gov).

Expert Opinion: Therapies targeting factors XI or XII can yield anticoagulant efficacy with the potential to reduce adverse bleeding. Advantages for targeting factor XI or XII include a wider therapeutic window and reduced bleeding. Long-term follow-up studies and a greater understanding of the safety and efficacy are required. Atrial fibrillation is a chronic disease and therefore the development of oral formulations is key.

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Anticoagulant; antibody; antisense oligonucleotide; atrial fibrillation; clotting factor; intrinsic pathway; clinical trial; novel; small molecule; stroke; thromboembolism; fxi; fxii; therapeutics

1. Introduction

Atrial fibrillation (AF) without significant valve disease (commonly referred to as non-valvular AF) is the most common cardiac arrhythmia worldwide and is a major burden to healthcare services [1,2]. Advancing age is a direct risk factor for AF, and with global population aging increasing at an accelerated rate, the prevalence of AF is also expected to rise as a result [3]. Current estimates indicate that the prevalence of AF in people over 40 years of age is 2.3%, rising to 5.9% in those over 65 years old [4]. Further concerns arise when we also consider that the incidence of ischemic stroke in patients with AF increases nearly five-fold compared to those patients without AF [5]. The most important contributory mechanism to this is thought to be thromboembolism.

Originally proposed in the nineteenth century by Rudolph Virchow, it is now widely accepted that 3 factors contribute toward thrombosis. These 3 factors, known as the Virchow triad, are: (1) abnormal blood flow and stasis, (2) vessel wall abnormalities (e.g. structural heart disease and endothelial damage/dysfunction), and (3) abnormal blood constituents (e.g. clotting factors and platelet abnormalities) [6–8]. There is extensive evidence that these abnormal changes are also evident in AF, suggesting that AF confers a prothrombotic state, thus promoting thrombosis [9–11].

Anticoagulant drugs such as heparin, low-molecular-weight heparins, and vitamin K antagonists (VKAs) have been used for decades by clinicians to treat or prevent thromboembolic disorders [2,12]. VKAs (e.g. warfarin) have also been the standard therapy for AF patients at high-risk of stroke and thromboembolism [13]; however, in routine clinical settings, VKAs are prescribed with caution and may potentially be inappropriate in some patients due to slow onset and offset of action, food and drug contraindications, an increased risk of bleeding, and the need for regular monitoring and maintenance for anticoagulation optimization [14,15]. Given the various limitations of VKAs, clinical development has identified new classes of anticoagulant therapies such as non-vitamin K antagonist oral anticoagulants (NOACs). Examples of NOACs include dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban. NOACs work to directly inhibit a single clotting enzyme; dabigatran inhibits thrombin, whereas rivaroxaban, apixaban, edoxaban, and betrixaban inhibit activated clotting factor X (FXa) [16]. A key advantage of NOACs compared to VKAs is that NOACs have a rapid onset of action and peak plasma levels are achieved between 1 and 4 hours after oral administration, whereas VKAs have an extended half-life of 60–72 hours and can take approximately 6 days to exert their full efficacy [16,17]. NOACs are believed to overcome the limitations of VKAs and this therefore makes them more manageable and safer for patient use [18]; however, patients prescribed NOACs still experience bleeding events

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Article highlights

- There is a significant increase in ischemic stroke risk in patients with atrial fibrillation.
- The vitamin K antagonist warfarin is a key antithrombotic agent which is prescribed to patients with atrial fibrillation to decrease the risk of stroke. Warfarin has a narrow therapeutic index and requires constant monitoring. The risk of bleeding is a common adverse effect, making warfarin a problematic therapy.
- Non-vitamin K antagonist oral anticoagulants have increased safety; however, bleeding is still an adverse effect.
- The inhibition of clotting factors XIa and XIIa of the intrinsic coagulation pathway is believed to be a safer alternative target to prevent thrombus formation. Such therapies are being investigated for safety and efficacy in phase I, and phase II clinical trials.
- Monoclonal antibodies (MAA868, osocimab, xisomab 3G3, garadicimab, and AB054) bind specifically to factor XI, XII, or the activated states (XIa and XIIa, respectively), preventing downstream activation in the coagulation cascade.
- Antisense oligonucleotides (IONIS-FXIRx and IONIS-FXI-L_{RX}) inhibit factor XI to decrease protein expression levels.
- Small molecule drugs (BMS-986,177, EP-7041, and LUNAC Therapeutics) are active-site inhibitors of factor XIa or XIIa.
- Novel precision oral anticoagulants (PROAC; VE-1902 and VE-2851) are selective and potent direct thrombin inhibitors.
- Many factor XIa and XIIa-inhibiting therapeutics are progressing through clinical trials and may become future options for patients with atrial fibrillation. It is possible that they will be included in treatment predictor scores for anticoagulation therapies.

This box summarizes key points contained in the article.

and therefore the risk has not been completely removed by their introduction [19].

The intrinsic pathway of coagulation has recently gained interest as a target candidate for potential therapeutics with comparably less risk of bleeding than agents currently on the market [20]. Research using FXII-deficient mice demonstrated that FXII is essential for thrombus formation and identified FXII as a novel target for antithrombotic therapy [21].

Considering the above information, the objectives of this review are to:

a. Discuss the limitations of current anticoagulants and the unmet clinical need that drives the search for the 'ideal' anticoagulants.
b. Discuss targeting of the intrinsic pathway for anticoagulation.
c. Discuss novel anticoagulants targeting activated FXI(a) and activated FXII(a).
d. Summarize the limitations and developmental issues of novel anticoagulants.

2. Current treatments for thrombosis

Approved in 1954, warfarin has remained as one of the main therapies to treat or prevent thromboembolic disorders [22]. In AF, warfarin-therapy patients result in a 64% reduction in total stroke rate and a 22% reduction in mortality compared to placebo or control [23] and, due to its success, more than 30 million prescriptions for warfarin are written in the United States alone per year [24].

Warfarin is a VKA and, as described in Figure 1, its mode of action is to interfere with the hepatic synthesis of the procoagulant vitamin K-dependant clotting factors II, VII, IX and X, as well as the synthesis of the anticoagulant proteins C, S and Z [14]. These clotting factors undergo gamma-carboxylation of glutamic acid residues at the NH2-terminal molecular region [25] which requires the presence of the reduced and active form of vitamin K, which makes these coagulation factors fully functional (enabling them to be active following proteolytic cleavage). Under normal conditions, vitamin K epoxide reductase complex 1 (VKORC1) converts vitamin KO, the oxidized and inactive form of vitamin K, into the active vitamin KH2 form [25,26]. This provides a continuous supply of vitamin KH2 causing clotting factor synthesis. Warfarin specifically inhibits VKORC1 causing an accumulation of inactive vitamin KO, and effectively reduces the fully functional hepatic synthesis of vitamin K dependent clotting factors as well as proteins C, S and Z [25].

Warfarin is often associated, however, with serious adverse effects, including bleeding and significant hemorrhage, thus limiting its therapeutic use. Furthermore, warfarin treatment requires frequent blood tests and monitoring to ensure patients are kept within the therapeutic range [27]. Patients are also required to adhere to certain dietary restrictions [28]. Analysis has shown that the annual rate of major bleeding was 1.3% in warfarin-treated patients, with a 0.3% risk of intracranial hemorrhage. Furthermore, the risk of death from a major bleed ranges from 13% to 33% [29]. Therefore, adherence and persistence with warfarin can be problematic, and cessation of therapy is associated with poor outcomes [30]. VKAs are challenging to use in clinical practise for the following reasons as they have a narrow therapeutic window, exhibit considerable variability in dose response among patients due to genetic factors, are subject to interactions with drugs and diet, the laboratory control is difficult to standardize and the maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics (PK) and pharmacodynamics (PD) of warfarin and good patient communication [25].

Previous studies have highlighted the risk of hemorrhagic complications in patients taking warfarin anticoagulation therapy. One population-based cohort study reported a 3.8% major bleeding rate per person-year over a 5-year follow-up period [31].

An important consideration to take into account is the observation that many patients diagnosed with AF have at least one existing comorbidity [32]. One study showed that 98% of 1297 participants, all of which were diagnosed with AF, had at least one additional condition [33]. A history of congestive heart failure, cerebrovascular disease, hepatic disease, renal disease, and diabetes mellitus are all comorbid medical conditions that have been associated with increased risks from bleeding on anticoagulant treatment [34]. Furthermore, at least 30 genes have been associated with warfarin metabolism

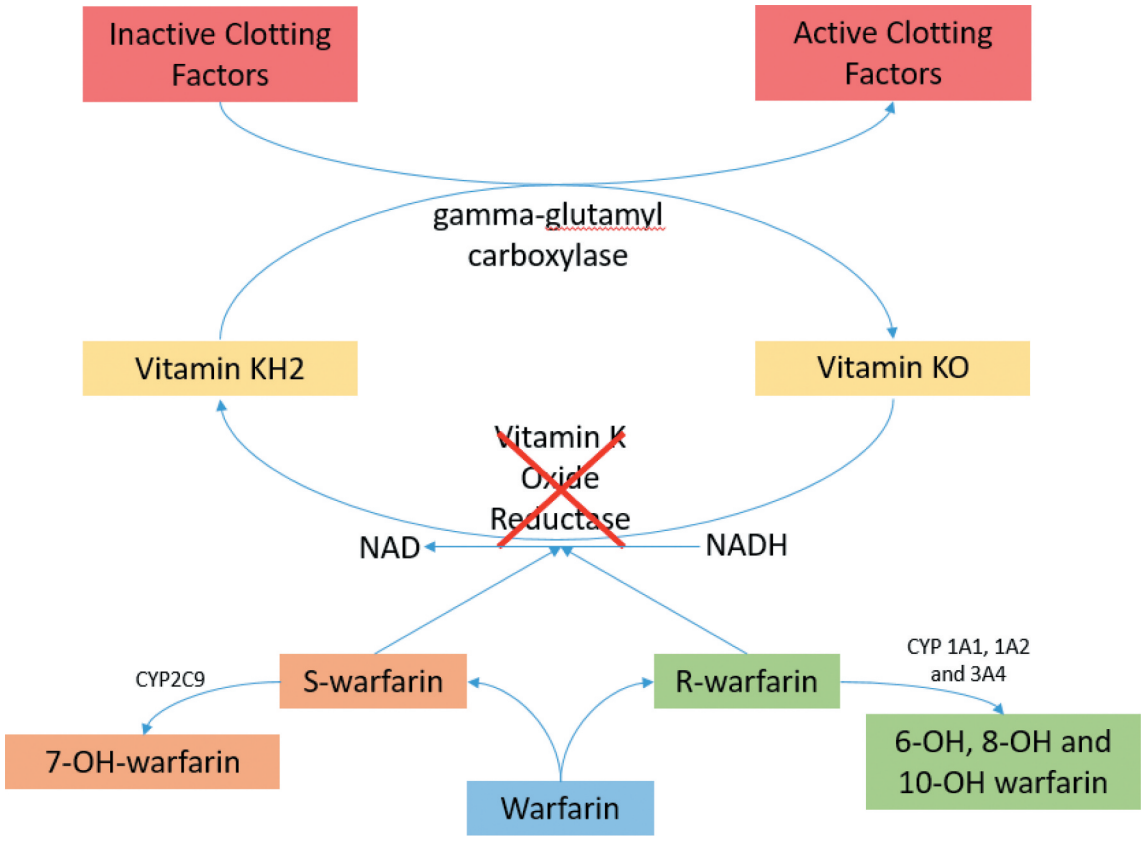

Figure 1. **The Mechanism of Action of Warfarin**. During the vitamin K cycle, the reduced form of vitamin K (vitamin KH_2) is oxidized to vitamin KO by the action of gamma-glutamyl carboxylase. Inactive coagulation factors, such as prothrombin, FVII, FIX, and FX, and the physiological anticoagulant proteins C and S, undergo post-translational carboxylation in the liver before secretion into the plasma. Vitamin KO is then reduced to vitamin KH2 by the action of vitamin K oxide reductase, whilst NADH gets converted into NAD. Warfarin – clinically available as an equal mixture of R and S enantiomers – inhibits vitamin K oxide reductase and therefore prevents vitamin KO reduction to vitamin KH2. S-warfarin is metabolized exclusively by CYP2C9 to 7-hydroxywarfarin, whereas CYP1A1, 1A2, and 3A4 are responsible for metabolizing R-warfarin to 6-hydroxywarfarin, 8-hydroxywarfarin and 10-hydroxywarfarin.

and action. Polymorphisms in genes encoding VKORC1 and cytochrome p-450-2C9 enzyme (CYP2C9) are responsible for approximately 40% of inter-individual variations in warfarin dose requirements [35]. Genetic polymorphisms could further predispose patients to a higher risk of bleeding when prescribed warfarin.

Given the various limitations of VKAs, research has focused on identifying new classes of anticoagulant therapies that overcome these adverse reactions and provide safer alternatives for patients. This era of anticoagulant development initially resulted in the discovery of NOACs, targeting thrombin (dabigatran) or activated FX (FXa; rivaroxaban, apixaban, edoxaban and betrixaban). These developments are now well supported by large randomized trials and 'real world' observational data [18,36–39]; however, a study aimed to evaluate bleeding risks in clinical practice in patients with AF being prescribed dabigatran, rivaroxaban, or apixaban compared with warfarin showed that the risk of gastrointestinal bleeding was higher with rivaroxaban and dabigatran compared with warfarin [40]. This data shows that bleeding events still occur in patients prescribed with NOACs [41]. The reason that bleeding is observed in current anticoagulant agents is that the targets for these agents are located in the common pathway of coagulation and are involved in both the formation of thrombosis and the stemming of bleeding. Therefore, a balancing act is required to achieve the optimal level of anticoagulation without a potential bleed. Considering the variability of the PK properties of these drugs between patients, achieving the single optimal dose for all patients remains a challenge. As a result, patients on NOACs still suffer thrombotic episodes (2.2–3.8%) and bleeding events (3.6–20.7%) with some resulting in death [42]. Many of the advantages and disadvantages of NOACs over VKAs are discussed in Table 1.

The mechanisms for bleeding events with NOACs have attracted much interest. For example, inhibition of FXa by rivaroxaban has anti-platelet effects through the inhibition of FXa-driven platelet activation via protease-activated receptor-1 (PAR-1), which reduces arterial thrombosis; conversely, this inhibition mechanism may also contribute to bleeding diathesis [51].

3. Stroke risk and thromboprophylaxis for patients with atrial fibrillation

There is a large degree of variability in stroke risk in patients with AF which is dependent on comorbidities and the use of antithrombotic therapies. Subpopulations of AF patients have

Table 1. **Advantages and disadvantages of NOACs compared to VKAs**. NOAC – Non-vitamin K antagonist oral anticoagulants, VKA – Vitamin K Antagonist, PK – Pharmacokinetics PD – Pharmacodynamics.

Advantages of NOACs over VKAs	Disadvantages of NOACs over VKAs
Few drug-drug interactions between NOACs and other drugs enabling concurrent use of other drugs in patients who are being treated with NOACs [43].	Caution should be considered when prescribing NOACs in patients with chronic kidney disease [44]. For example, approximately 80% of dabigatran is eliminated through the kidneys as an active drug, therefore those with chronic kidney disease may experience a minimum of a twofold increase in plasma elimination half-life [45].
NOACs are not associated with food interactions, especially those that contain vitamin K [46].	Apixaban and rivaroxaban are contraindicated by hepatic disease [45].
NOACs are characterized by predictable PK and PD [47].	There is an absence of a specific test which would be required in certain situations – such as the need for urgent surgical intervention, intravenous thrombolysis in acute ischemic stroke patients, intracerebral bleeding, and overdose. Anticoagulation assessment is necessary [48].
NOACs have a rapid onset and offset of action [49].	Some patients cannot afford NOACs [43].
Routine laboratory monitoring is not required [49].	They have a short half-live – If a patient forgets to take the NOAC their could potentially put their life at risk [43].
They have a short half-life – NOACs are advantageous emergency surgery and in cases of bleeding due to accumulation of the drug in the blood [50].	The absence of an affordable antidote is a problem in the case of spontaneous bleeding from overdose or in the case of traumatic injury which requires urgent surgical intervention [50].

annual stroke risk rates that range from less than 2% to more than 10% [52]. There are many stroke risk factors that have been proposed. The more common and validated ones have been used to formulate stroke risk scores, such as the CHA_2DS_2-VASc score [53–55], and take into consideration several parameters that contribute to the degree of disease severity and stroke risk (Table 2). The CHA_2DS_2-VASc score is used to determine the required course of either anticoagulation or antiplatelet therapy. Male patients with a CHA_2DS_2-VASc score of 0 and female patients with a CHA_2DS_2-VASc score of 1 are considered to be at low risk of stroke and therefore do not require anticoagulation [53,55]. Given that the default treatment for AF patients is stroke prevention unless categorized as 'low risk', all other AF patients with one or more stroke risk factors should be considered for stroke prevention, with a preference toward using a NOAC over VKAs. Despite a reduction in stroke risk with current anticoagulants there remains a residual risk of cardiovascular and cerebrovascular events, even in anticoagulated patients, as well as a risk of serious bleeding. This necessitates the quest for new options in delivering thromboprophylaxis with new drugs that offer better efficacy and safety compared to current agents. Even with new anticoagulant drugs, the default would remain that stroke prevention is needed unless low risk.

Table 2. **The CHA_2DS_2-VASc score system** [56].

	Condition	Point
C	Congestive Heart Failure	1
H	Hypertension – Blood pressure consistently above 140/90 mmHg	1
A_2	Age 75 years and over	2
D	Diabetes Mellitus	1
S_2	Prior stroke	2
V	Vascular disease	1
A	Age between 65 and 75 years	1
Sc	Sex category (female)	1

4. Current research targets

The intrinsic pathway, extrinsic pathway, common pathway, and the plasma kallikrein-kinin (KKS) system are important in producing prothrombotic activity which is critical for coagulation, as described in Figure 2 [57].

FXI is a serine protease that belongs to the intrinsic pathway. The zymogen, or precursor, is cleaved by FXIIa to form activated FXIa. FXI is an important factor in the generation of thrombin; however, overproduction of FXIa can result in an overproduction of thrombin which results in clot formation and thrombosis. It is therefore believed that an inhibition of FXIa, or a reduction in the level of FXI, offers a potential novel anticoagulant therapeutic target by preventing the progression of the intrinsic coagulation pathway without interfering with the extrinsic pathway. This would result in suppression of the propagation phase of fibrin formation via the intrinsic pathway to prevent thrombosis, whilst maintaining the hemostatic response [58].

An intact extrinsic pathway with deficiencies of FVIII or FIX results in a severe bleeding diathesis (hemophilia A for FVIII deficiency and hemophilia B for FIX deficiency) in a subset of patients. This renders FVIII or FIX as illogical drug targets but demonstrates the importance of the intrinsic pathway in coagulation. Deficiencies of FVIII, FIX, FXI and FXII cause a significant prolongation to a patient's clotting time when activated via the intrinsic pathway (activated partial thromboplastin time; aPTT). However, individuals with FXII deficiency do not suffer any bleeding abnormalities [59]. This observation begs the question – is FXII relevant for physiological hemostasis? It has been found that FXII deficient mice were protected from collagen and epinephrine-induced thromboembolism [21], suggesting that FXII is important for thrombus formation *in-vivo*, and this has made FXII stands out as a therapeutic target for thrombosis.

Figure 2 illustrates both the intrinsic and extrinsic pathways, with the extrinsic pathway being the shorter mode of secondary hemostasis. The extrinsic pathway is activated by external trauma which causes damage to the blood vessels, whereas the intrinsic pathway is activated by trauma within the vascular system [60]. Following external trauma, endothelial cells release tissue factor (TF) which activates FVII into FVIIa [60]. FVIIa then activates FX into FXa, at the point where both the extrinsic and intrinsic pathways meet, resulting in activation of the common pathway [60].

5. Phase I and Phase II clinical trials

There is much interest in the development of novel anticoagulants targeting FXIa and FXIIa [61,62], with the aim of identifying novel therapeutics capable of preventing

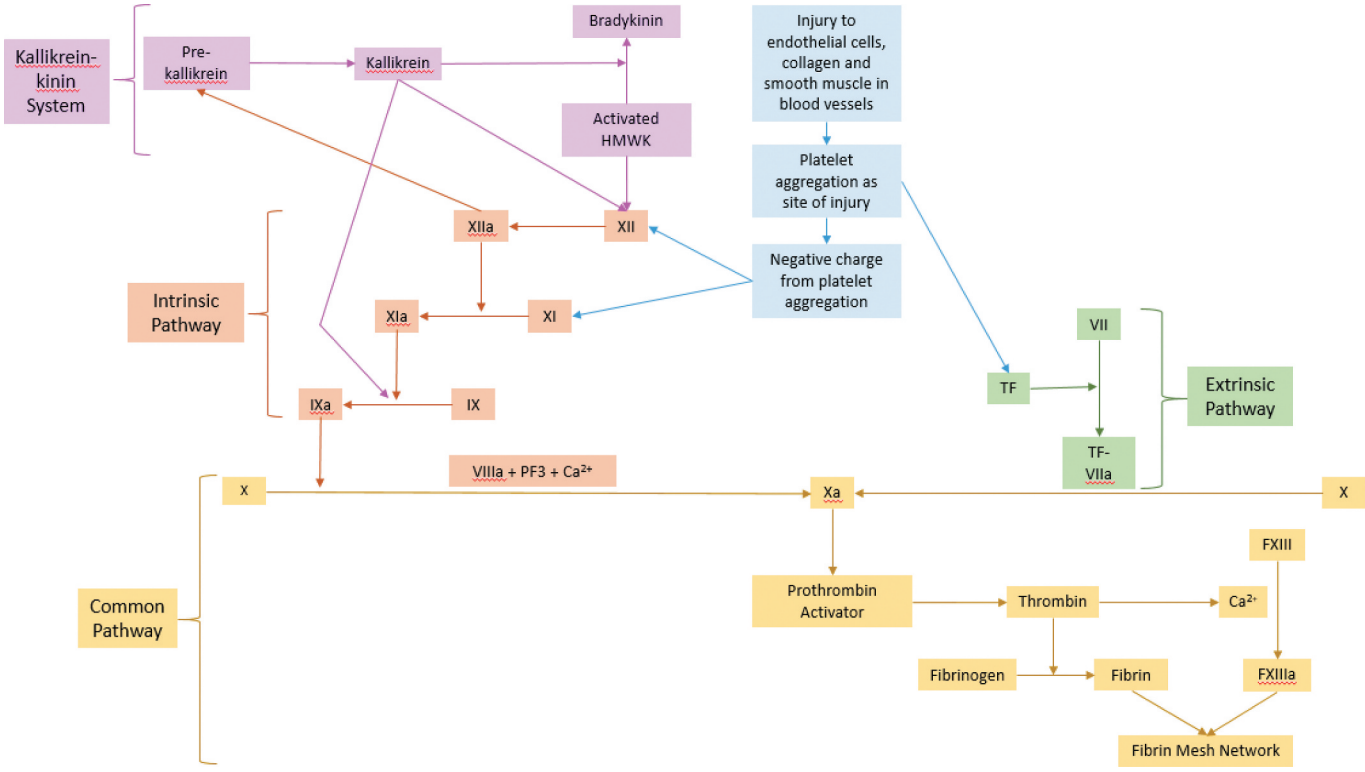

Figure 2. Schematic diagram of the human plasma kallikrein-kinin system, the intrinsic and extrinsic coagulation pathways, and the common pathway. Damage to endothelial cells, collagen, and vascular smooth muscle due to injury results in the production of the glycoprotein Von Willebrand Factor (VWF). Platelets bind to VWF via glycoprotein 1b (Gp1b), which causes them to secrete ADP and TXA2. This stimulates the platelets to translocate to the site of injury. Platelets therefore aggregate at the site of injury and are bound together by fibrinogen via GpIIa/IIIa, which forms a platelet plug. Phosphotidylserine (PS), a negatively charged aminophsospholipid, creates a negative charge on the membrane surface of activated platelets. During the intrinsic pathway, FXII interacts with these negative charges from the platelets and collagen and is activated to FXIIa. FXIIa then activates FXI to FXIa, which in turn activates FIX to FIXa. FVIII, along with PF3 Ca2+, interacts with FIXa to form a complex and activate FX to FXa. Tissue factor (TF) is also released from injured endothelial cells and damaged tissue cells. TF activates the extrinsic pathway, supporting the conversion of FVII to FVIIa. TF-FVIIa activates FX to FXa. The intrinsic and extrinsic pathways meet at the common pathway when FX is activated to FXa. FXa, FV, PF3, and Ca^{2+} activate prothrombin activator (FII) into thrombin (FIIa). Thrombin converts the soluble plasma protein fibrinogen into fibrin which polymerizes into soluble fibrin. Furthermore, thrombin converts FXIII, in the presence of Ca^{2+} to its activated form, FXIIIa. FXIIIa crosslinks fibrin to form an insoluble fibrin mesh network and prevents the platelet plug from becoming dislodged.

thrombus formation with minimal increased risk of hemorrhage. Pharmaceutical companies are now utilizing many different innovations to produce safer and more effective anticoagulants. This is evident from the variety of products currently in the clinical trial pipeline as well as those which are currently in pre-clinical, phase I, and phase II clinical trials. These categories include monoclonal antibodies, antisense oligonucleotides (ASO), and small molecules.

A list of novel antibodies, ASOs, and small molecules targeting FXI and FXII – including the compound name, developer, inhibitor class, target/action, stage of development, study identification, the number of patients in the study, and the study reference – is included in Table 3 and each will be discussed in turn below.

5.1. Novel antibody-based therapeutics preventing thrombosis

In 1975 Kohler and Milstein introduced the hybridoma technique which made it possible to obtain large amounts of pure monoclonal antibodies (mAbs) [63]. Due to their high specificity and affinity, there is widespread acceptance that humanized mAbs can be used as innovative therapeutic agents.

The use of mAbs as therapeutics requires the optimization of key attributes such as affinity, specificity, stability, solubility, and PK. To address these problems, the necessary safety measures, drug design techniques, and *in-vitro* screening methods have taken place.

5.2. Novel antibody therapeutics targeting FXI

5.2.1. MAA868

MAA868 is an antibody which binds to both FXI and FXIa [64]. The first-in-human phase I clinical trial comprised a 28-day screening period, 3-day baseline period, 7-day inpatient observation period, and an outpatient observation period of 9–106 days. Subjects either received MAA868 or a placebo subcutaneously at an 8:2 ratio for each dose cohort. Patients in the MAA868 group were administered single ascending doses of MAA868 from 5 mg up to 240 mg subcutaneously to determine safety and tolerability, as well as the PK and PD parameters. Results showed that administrations of up to 240 mg of MAA868 were safe and well-tolerated and resulted in sustained FXI inhibition for 4 weeks.

A phase II clinical trial (https://clinicaltrials.gov/ct2/show/NCT04213807), commenced in 2020, aims to evaluate the safety, tolerability, PK effects, and PD effects of MAA868 in

Table 3. Novel FXI, FXII and thrombin inhibitors in clinical trials.

Compound Name	Developer	Inhibitor Class	Target/Action	Stage of Development	ClinicalTrials.gov; Study ID	Population	Trial Design	Number of Patients	Reference
MAA868	Anthos Therapeutics	Fully human monoclonal IgG1 antibody	FXI and FXIa	Phase I	n/a	Healthy patients	Randomized, subject and investigator blinded placebo-controlled single ascending dose study	61 Patients	[64]
MAA868	Anthos Therapeutics	Fully human monoclonal IgG1 antibody	FXI and FXIa	Phase II	NCT04213807	Patients with Atrial Fibrillation or flutter at low risk of thromboembolic stroke or peripheral embolism	multicentre, randomized, subject and Investigator-blinded, placebo-controlled, parallel-group	48 patients	https://clinicaltrials.gov/ct2/show/NCT04213807
Osocimab/ BAY1213790	Bayer Pharmaceuticals	Fully human monoclonal IgG1 antibody	FXIa	Phase II	NCT03276143	Patients undergoing total knee arthroplasty	Randomized, open-label, adjudicator-blinded, phase 2 noninferiority trial with observer blinding for osocimab doses	600 Patients	[62]
BAY1831865	Aronora and Bayer Pharmaceuticals	Fully human monoclonal IgG1 antibody	FXI	n/a	n/a	n/a	n/a	n/a	
AB023/ Xisomab 3G3	Aronora	Fully human monoclonal IgG1 antibody	FXIa	Phase I	NCT03097341	Healthy Patients	Randomized, double-blind, placebo-controlled, single ascending bolus dose study	21 patients	[67]
AB023/ Xisomab 3G3	Aronora	Fully human monoclonal IgG1 antibody	FXIa	Phase II	NCT03612856	Patients with end stage renal disease on chronic hemodialysis	Randomized, Double-Blind, Placebo-Controlled Study	27 patients	https://clinicaltrials.gov/ct2/show/NCT03612856
Garadacimab/ CSL312	CSL Behring	Recombinant fully human monoclonal antibody	FXIIa	Phase II	NCT03712228	Patients with type I or type II hereditary angioedema	multicenter, randomized, double-blind, placebo-controlled, parallel-arm Phase 2 study	32 patients	https://haei.org/results-for-garadacimab-as-preventive-hae-treatment/
AB054	Aronora	Fully human monoclonal IgG1 antibody	FXII	Pre-Clinical	n/a	n/a	n/a	n/a	http://aronorabio.com/site/pipeline/
IONIS-FXIRx /IONIS-416,858/ISIS-416,858/ BAY-2,306,001	IONIS and Bayer	Antisense Oligonucleotide	Reduce hepatic synthesis of FXI by inducing catalytic degradation of FXI mRNA	Phase II	NCT03358030	Patients undergoing elective primary unilateral total knee arthroplasty	Randomized, Double-Blind, Placebo-Controlled	300 patients	[20]
IONIS-FXI-L_{RX}	IONIS and Bayer	Antisense Oligonucleotide	Reduce hepatic synthesis of FXI by inducing catalytic degradation of FXI mRNA	Phase I	NCT03582462	Healthy Patients	double-blind, randomized, placebo-controlled, dose-escalation study conducted at a single center	66 patients	https://ir.ionispharma.com/node/25266/pdf https://ir.ionispharma.com/static-files/2ecdbe5e-981d-4fab-ba01-16e04a5e3227 https://clinicaltrials.gov/ct2/show/NCT03582462
BMS-986,177 or JNJ-70,033,093	Janssen of Johnson and Johnson and Bristol-Myers Squibb	Small molecule	FXIa inhibitor	Phase II	NCT03891524	Patients undergoing Elective Total Knee Replacement Surgery	Randomized, Open-Label, Study Drug-Dose Blind, Multicenter Study	Estimated 1200 patients	https://clinicaltrials.gov/ct2/show/NCT03891524
EP-7041	eXithera	Small molecule	FXIa inhibitor	Phase Ia/IIb	NCT02914353	Healthy patients	Randomized, Double-Blind, Placebo-Controlled	48 patients	https://clinicaltrials.gov/ct2/show/NCT02914353 [80]

(*Continued*)

Table 3. (Continued).

Compound Name	Developer	Inhibitor Class	Target/Action	Stage of Development	ClinicalTrials.gov; Study ID	Population	Trial Design	Number of Patients	Reference
In development	LUNAC Therapeutics	Small molecule	FXIIa inhibitor	Preclinical	n/a	n/a	n/a	n/a	https://www.lunactherapeutics.com/
VE-1902	Verseon	Small molecule	direct thrombin inhibitor	Phase I	n/a	Healthy Patients	single-center, double-blinded, randomized, placebo-controlled study	100–120 patients	https://www.invasivecardiology.com/news/verseon-reports-first-dosing-phase-1-trial-new-precision-oral-anticoagulant
VE-2851	Verseon	Small molecule	direct thrombin inhibitor	n/a	n/a	n/a	n/a	n/a	https://www.invasivecardiology.com/news/verseon-reports-first-dosing-phase-1-trial-new-precision-oral-anticoagulant

patients with AF flutter, who are at low risk of thromboembolic stroke, or peripheral embolism. The trial is to be split into 4 cohorts of either a placebo, low dose MAA868, high dose MAA868, and a dose of MAA868 that was yet to be determined at the time of publication. The concentrations of MAA868 in this study had not been disclosed prior to the submission of this review for publication.

5.2.2. Osocimab (*aka BAY1213790*) and BAY1831865

Osocimab is an antibody which entered phase I clinical trials [65,66] in 2020. During the trial, healthy male volunteers were administered 1 of 9 escalating doses of intravenous osocimab at 0.015 mg/kg, 0.06 mg/kg, 0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.25 mg/kg, 2.5 mg/kg, 5 mg/kg, or 10 mg/kg, or a placebo. Subjects were followed up on days 14, 21, 28, 56, 84, and 150 in which safety PK and PD were determined [66]. The results showed that all doses of osocimab had favorable safety profiles as there were no observed cases of bleeding. Furthermore, osocimab administration was associated with increased aPTT and thromboelastometry (previously rotational thromboelastometry; ROTEM), suggesting that clotting took longer to occur in test subjects versus those receiving the placebo.

The phase II clinical trial for osocimab, entitled FOXTROT, compared osocimab against enoxaparin and apixaban in patients at risk of postoperative venous thromboembolism (VTE) undergoing knee arthroplasty https://clinicaltrials.gov/ct2/show/NCT03276143. Results showed that postoperative osocimab doses at 0.6 mg/kg, 1.2 mg/kg, and 1.8 mg/kg had lower efficacy than enoxaparin however, primary outcome of incidence of VTE at 10 to 13 days postoperatively showed that a preoperative dose at 1.8 mg/kg was superior to enoxaparin.

Importantly, the study showed that no clinically relevant bleeding events were observed at doses 0.6 mg/kg and 1.2 mg/kg of osocimab; however, post-operative and pre-operative doses of osocimab at 0.3 mg/kg did not meet the pre-specified criteria for non-inferiority with risk differences of 2.6% and −3.6%, respectively. Major or clinically relevant non-major bleeding was also observed in up to 4.7% of the patients receiving osocimab, 5.9% receiving enoxaparin, and 2% receiving apixaban [62].

BAY1831865, like osocimab, is a FXIa/FXI inhibitor for use in the treatment of thrombosis [65]; however, it has not had clinical trial details endorsed.

5.2.3. Xisomab 3G3 (*aka AB023*)

During phase I clinical trials to test the safety and efficacy of xisomab [67], subjects received doses of the drug at either 0.1 mg/kg, 0.5 mg/kg, 2 mg/kg, 5 mg/kg xisomab 3G3, or a placebo to analyze the PK effects, PD effects, and safety. Plasma xisomab 3G3 was detectable in all subjects 0.08 hours post infusion and remained detectable in the majority of subjects up to 120 hours after treatment. At the higher doses of 2 mg/kg and 5 mg/kg, xisomab 3G3 remained detectable in all subjects throughout 672 hours of sampling. There were no major adverse events experienced by participants which suggests that xisomab 3G3 was safe and well tolerated. A prolonged aPTT in a dose-dependent manner was observed, but prothrombin time and bleeding times were not altered, suggesting no off-target effects on the extrinsic pathway [67].

Xisomab 3G3 completed phase II clinical trials in 2020, during which the safety and efficacy of the drug was evaluated in patients with end stage renal disease on chronic hemodialysis https://clinicaltrials.gov/ct2/show/NCT03612856. During the trial, patients were treated with xisomab 3G3 at 0.25 mg/kg, 0.5 mg/kg, or a placebo. Results from this trial had not been released prior to the submission of this review for publication.

5.3. Novel antibody therapeutics targeting FXII

5.3.1. Garadacimab (*aka CSL312*)

The antibody inhibitor garadacimab entered phase II clinical trials in October 2018 as a preventative treatment in hereditary angioedema (HAE) https://www.clinicaltrials.gov/ct2/show/NCT03712228 [68]. In this study, subjects were treated with either garadacimab at 75 mg, 200 mg, 600 mg, or a placebo to determine the efficacy, PK effects, and safety. Results from the study showed that garadicimab was well tolerated in patients and also showed significant mean percentage reductions in HAE attacks compared to the placebo [69].

5.3.2. AB054

AB054 is a FXII antibody inhibitor [70] which, as of 2020, is being analyzed in preclinical studies. Details about its structure and how it inhibits FXII had not been released prior to the submission of this review for publication.

5.4. Novel Antisense Oligonucleotides (ASOs) therapeutics preventing thrombosis

ASOs are stretches of RNA complementary to the gene of interest. The ASO binds to cellular mRNA and prevents the translation of the gene of interest, inhibiting its expression and thereby reducing the level of protein expressed [71]. ASOs therefore, by definition, are designed to decrease the expression of the clotting protein of interest. There have been successful studies in animal models which show the presence of anticoagulation and a decreased bleeding risk compared to warfarin [72]. As a result, there is much interest in investigating the effects of ASOs in a clinical environment. The following ASOs detailed below have been entered into clinical trials, although the full details of the outcome had not been made available prior to the submission of this review for publication.

5.5. Novel antisense oligonucleotides therapeutics targeting FXI

5.5.1. IONIS-FXI$_{RX}$ (*aka IONIS-416,858/ISIS-416,858/BAY-2,306,001*)

IONIS-FXI$_{RX}$ is an ASO which entered phase IIb clinical trials in November 2017 [20]. The trial will determine the PK of IONIS-FXI$_{RX}$ in patients with end-stage renal disease on hemodialysis to prevent thrombosis https://clinicaltrials.gov/ct2/show/NCT03358030. Although trial results were not available prior to the submission of this review for publication, it has been suggested that IONIS-FXI$_{RX}$ 'demonstrated robust reductions in FXI activity and no treatment-related major bleeding' [73].

5.5.2. IONIS-FXI-L_{RX}

IONIS-FXI-L_{RX} is a second generation ligand-conjugated antisense ASO drug designed to reduce the production of FXI in the liver [74]. IONIS-FXI-L_{RX} is a modified version of IONIS-FXI_{RX}. The safety, tolerability, PK effects, and PD effects of IONIS-FXI-L_{RX} were deduced in a phase I clinical trial in which IONIS-FXI-L_{RX} was administered to healthy volunteers. Results for this trial had not been published prior to the submission of this review for publication; however, it is of note that IONIS's partner, Bayer, has decided to advance IONIS-FXI-L_{RX} into a phase II clinical trials [74].

5.6. Novel small molecule therapeutics targeting FXI and FXII preventing thrombosis

Small molecules have an upper molecular weight limit of approximately 900 Daltons, allowing them to rapidly diffuse across cell membranes so that they can reach intracellular sites of action [75]. Small molecules are able to inhibit the specific actions of multifunctional proteins or disrupt protein–protein interactions [76]. A key advantage of small molecule drugs is that many of them can be taken orally, whereas biologic drugs generally require injection or other parenteral administration [77]. Oral small molecule drugs administered to patients typically have rapid onset and offset of action. In the interest of FXI and FXII, small molecule drugs block the active site or alter the shape of the active site [78].

FXI is a polypeptide with a dimeric structure. It contains a trypsin-like domain with 4 apple domains (A1 to A4). FXI is the product of a gene duplication for prekallikrein, and therefore has similar structural features to prekallikrein. Due to the structural similarities of the trypsin-like catalytic domain between FXIa and kallikrein, it is essential that any small molecule targeting only FXIa is highly selective and does not have promiscuous qualities [79].

5.7. Novel small molecule therapeutics targeting FXI

5.7.1. BMS-986,177 (aka JNJ-70,033,093)

BMS-986,177 is a small molecule in phase II clinical trials https://clinicaltrials.gov/ct2/show/NCT03891524. The purpose of the study is to determine the efficacy of BMS-986,177 in preventing total VTE in patients undergoing elective total knee replacement surgery. The clinical trial was still ongoing at the time that this review was submitted for publication and therefore the results had not yet been released.

5.7.2. EP-7041

EP-7041 is a small molecule FXI inhibitor which completed phase Ia/Ib clinical trial as of June 2018 [80]. During EP-7041's first-in-human study, healthy volunteers received either a single intravenous ascending dose of EP-7041 from 0.01 mg/kg up to 1.0 mg/kg, or a continuous intravenous infusion of EP-7041 for 5 days from 0.01 mg/kg/hr up to 0.6 mg/kg/hr. Per cohort, 6 subjects received EP-7041 and 2 received a matched – dose placebo. PK effects, PD effects, aPTT, and safety were determined. The results of the study showed no serious side effects; however, mild headaches were reported in 23% of the patients. Parenteral EP-7041 showed favorable, dose-proportional PK with rapid onset, rapid offset, and predictable dose-related increases of aPTT. Ultimately, EP-0741 showed selective inhibition of FXI with antithrombotic effect with minimal risk of bleeding [80].

5.8. Novel small molecule therapeutics targeting FXII

As of 2020, a small molecule FXIIa inhibitor by LUNAC Therapeutics [81] is in preclinical development; however, the structure of the therapeutic and how it inhibits the active site of FXIIa had not been released prior to the submission of this review for publication.

5.9. Novel small molecule therapeutics targeting thrombin

Verseon has announced two novel precision oral anticoagulants (PROAC) – VE-1902 and VE-2851 – which are selective, potent direct thrombin inhibitors [82]. VE-1902 is believed to have a particularly unique pharmacological profile due to its covalent mechanism of action [83]. It acts to selectively inhibit thrombus formation whilst leaving thrombin-mediated platelet function largely unaffected. It also inhibits thrombin formation without significantly delaying the initiation phase of the clotting cascade. This novel mechanism is believed to be the reason as to why inhibited thrombus formation is responsible for the reduced bleeding in the models tested [83]. These novel PROACs are believed to be particularly advantageous as they are suitable for long-term co-administration. VE-1902 was in phase I clinical trials at the time that this review was submitted for publication and was being trialed in healthy volunteers, whereas VE-2851 was due to begin clinical trials in 2021.

6. Conclusion

AF is the most common sustained arrhythmia. It is associated with significant patient morbidity and mortality chiefly because of the increased risk of associated thromboembolic complications. Patients with AF have a 5-fold increased risk of stroke; in fact, 20–30% of all strokes are attributed to this arrhythmia. Therapeutic anticoagulation offers clinical benefits to patients; however, these benefits are associated with significant adverse effects. Initiation and continuation of anticoagulation therapy thus requires routine screening, but this can significantly impact healthcare systems and service providers and the patient quality of life. Consequently, research is directed toward safer pharmacological approaches than those offered currently. A lower risk of adverse effects and a similar efficacy to current agents is desired, as is observed with VKAs and NOACs.

Many of the therapeutics discussed in this paper are, or have been, validated for clinical proof-of-concept as agents which can prevent thrombosis in patients undergoing total knee replacement surgery. Therefore, it would be beneficial to understand the potential of the novel anticoagulants in those patients who have AF and who are at serious risk of thrombosis. This would enable researchers to deduce the effectiveness and safety of these drugs in this setting. Other aspects to

consider include the potential for drug–drug interactions and, given that many patients with AF have renal impairment, there is the necessity to assess renal clearance and the key challenges if used in patients with end stage renal failure. For this reason, the outcome of the mAb MAA868 clinical trials as the only novel FXI/FXII inhibitor being trialed in patients with AF [at the time of this publication] is eagerly awaited.

mAbs are innovative therapies because of their specificity, efficacy, and safety; however, there are concerns regarding immunogenicity and they will hence require assessment during the development process. The rapid onset of action and increased associated half-life of mAbs confers clinical advantages such as potential reductions in dose frequency and the number of missed appointments by patients. The slow offset action of mAbs could have significant implications if a reversal of the administered therapeutic was required. The safety of mAbs must therefore be considered as a high priority before their general administration.

From a practical perspective, it would be more advantageous for patients and service providers if novel FXI/FXII inhibitors intended for long-term use were developed as an oral formulation. Initial intravenous formulation may allow for acute administration, especially if the patient is unable to take oral medications post-operatively. This approach could later be converted to oral therapy for the long-term management of a more chronic state. With emerging intrinsic pathway targeting, the treatment of patients with a lower risk of adverse bleeding would be a paradigm shift in anticoagulation therapy.

7. Expert opinion

With life expectancy increasing, there is an urgent need to develop safer anticoagulation agents to meet the needs of patients. The global prevalence of AF is 37,574 million cases (0.51% of the world population) [84] which is coupled with a 5-fold increase in the prevalence of ischemic stroke. Despite current therapeutics being effective, anticoagulants come with the potential of serious adverse reactions including extensive bleeding.

The alarming rise in the number of patients with AF has propelled research into safer alternative pharmacological agents. Research has shown that FXI and FXII are promising drug targets for the prevention of thrombosis with a marked reduction in risk of bleeding.

The development of targeted monoclonal antibodies, antisense oligonucleotides, and small molecule inhibitors is in progress; several are in phase I or phase II trials.

Preclinical and early clinical studies suggest that therapies targeting the intrinsic pathway can yield anticoagulant efficacy with potential to reduce the incidence of bleeding. Further studies are required to determine whether comorbidities and common genetic, lifestyle, or environmental factors in this subset of patients can result in an increase in the risk of bleeding.

As first-in-class agents, it will be interesting to monitor the clinical effects of targeting either FXI or FXII, especially with respect to any effects on inflammatory pathways. It is possible that reduced conversion of prekallikrein to kallikrein by FXIIa may occur with FXIIa inhibitors, thereby modulating inflammation by inhibiting bradykinin generation which may lead to further beneficial clinical effects. Kallkrein has recently been shown to directly activate FIX [85–88]. This second mechanism implies that a further reduction of thrombin generation via direct kallikrein activation of FIX, independent of FXI, may be possible with FXIIa inhibitors.

It will be important to assess the long-term effects of the novel FXI and FXII – targeting therapeutics. Therefore, long-term follow-up should be considered by all those conducting clinical studies. A key safety precaution with antibody and small molecule approaches will be to identify agents which are capable of reversing their mechanism of action if an adverse bleeding event occurs. Although, if FXIIa and FXIa inhibitors follow the phenotype of FXII or FXI deficient individuals, it would be anticipated that there will be fewer bleeding events observed with FXIIa inhibitors compared with FXIa inhibitors.

Another challenge that may be observed with FXIa inhibitors is the therapeutic window for efficacy versus bleeding. As observed with the ASO clinical trial for FXI, there seems to be a narrow window of FXI reduction to achieving efficacy [20]. In contrast, potential complete inhibition of FXIIa could in principle be possible without compromising on bleeding and therefore a wide therapeutic window could be achieved.

Practical considerations to improve a patient's quality of life must also be considered when developing new therapeutics. AF is a global, chronic condition with some portions of the population having more favorable advantages over others – for example, there may be economical and geographical impracticalities with requiring patients to attend monthly clinics in some parts of the world with less advanced healthcare systems and socioeconomic development. Such a requirement has the potential to reduce patient compliance with adhering to the necessary treatment schedule in order to manage their condition effectively and safely.

In order to gain more confidence in the efficacy and safety of the novel therapeutics discussed here, it is essential that when phase II trials proceed to phase III, the selected patient cohorts accurately represent the observed patient population in terms of age, gender, race, existing comorbidities, and long-term therapeutic use. This will provide more realistic safety and efficacy data and result in greater understanding of the novel anticoagulants, ASOs, mAbs, and small molecule anticoagulants. There appears to be great potential for these new therapeutic avenues; however, due caution must be used and safety and efficacy profiles diligently obtained to ensure patient safety. Should there be superior safety and efficacy within the novel FXI and FXII inhibiting therapeutics compared to the NOACs, it is very likely that the new generation of anticoagulants could replace standard existing therapies.

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Abbreviations

AF - atrial fibrillation
VKA - vitamin K antagonists

NOAC - non-vitamin K antagonist oral anticoagulants
VKORC1 - vitamin K epoxide reductase complex 1
PK - pharmacokinetics
PD - pharmacodynamics
CYP2C9 - cytochrome p-450-2C9 enzyme
PAR-1 - protease-activated receptor-1
KKS - kallikrein-kinin system
aPTT - activated partial thromboplastin time
TF - Tissue Factor
ASO - antisense oligonucleotides
mAb - monoclonal antibodies
ROTEM - rotational thromboelastometry
VTE - venous thromboembolism
HAE - hereditary angioedema
PROAC - precision oral anticoagulants

Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Patel NJ, Atti V, Mitrani RD, et al. Global rising trends of atrial fibrillation: a major public health concern. Heart. 2018;104(24):1989.
2. January CT, Wann SL, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. Circulation. 2019;140(2):e125–e151.
3. Heeringa J, van der Kuip DA, Hofman A, *et al*. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006;27(8):949–953.
   • **European Epemiological study on the burden associated with atrial fibrillation.**
4. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. JAMA Intern Med. 1995;155(5):469–473.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22 (8):983–988.
6. Keren G, Etzion T, Sherez J, *et al*. Atrial fibrillation and atrial enlargement in patients with mitral stenosis. Am Heart J. 1987 Nov;114 (5):1146–1155.
7. Sanfilippo AJ, Abascal VM, Sheehan M, *et al*. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. Circulation. 1990 Sep;vol. 82(no. 3):pp. 792–7.
8. Masawa N, Yoshida Y, Yamada T, et al. Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of macroscopically visible thrombi. (in eng), Virchows Arch A Pathol Anat Histopathol. 1993;4221:67–71.
9. Shirani J, Alaeddini J. Structural remodeling of the left atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol. 2000 Mar-Apr;9(2):95–101.
10. Lip GY, Lip PL, Zarifis J, *et al*. Fibrin D-dimer and beta-thromboglobulin as markers of thrombogenesis and platelet activation in atrial fibrillation. Effects of introducing ultra-low-dose warfarin and aspirin. Circulation. 1996 Aug 1;94(3):425–431.
11. Goldman ME, Pearce LA, Hart RG, *et al*. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: i. Reduced flow velocity in the left atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). J Am Soc Echocardiogr. 1999 Dec;12(12):1080–1087.
12. Franchini M, Liumbruno GM, Bonfanti C, et al. The evolution of anticoagulant therapy. (in eng), Blood Transfus. 2016;142:175–184.
13. Lip GYH, Banerjee A, Boriani G, *et al*. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. CHEST. 2018;154(5):1121–1201.
   • **Recent evidence-based guidelines on antithormbotic manegement of atrial fibrillation.**
14. Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines,". Chest. 2012 Feb;141(2):e44S–e88S.
15. Amouyel P, Mismetti P, Langkilde LK, et al. INR variability in atrial fibrillation: a risk model for cerebrovascular events. Eur J Intern Med. 2009 Jan;20(1):63–69.
16. Klauser W, Dütsch M. Practical management of new oral anticoagulants after total hip or total knee arthroplasty. Musculoskelet Surg. 2013 Dec;97(3):189–197.
17. Kahlon P, Nabi S, Arshad A, et al. Warfarin Dosing and Time Required to Reach Therapeutic International Normalized Ratio in Patients with Hypercoagulable Conditions. (in eng), Turk J Haematol. 2016;334:299–303.
18. Hohmann C, Hohnloser SH, Jacob J, et al. Non-Vitamin K Oral Anticoagulants in comparison to phenprocoumon in geriatric and non-geriatric patients with non-valvular atrial fibrillation. Thromb Haemost. 2019 Jun;119(6):971–980.
19. Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. Clin Res Cardiol. 2017 Aug;106(8):618–628.
20. Büller HR, Gailani D, Weitz JI. Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis. N Engl J Med. 2014;372 (3):232–240.
   •• **Important Phase II trial of the Factor XI antisence oligonucleotide for VTE prevention.**
21. Renné T, Pozgajová M, Grüner S, *et al*. Defective thrombus formation in mice lacking coagulation factor XII. Vol. 202. ed: The Rockefeller University Press; 2005.
22. Johnson ME, Lefèvre C, Collings SL, *et al*. Early real-world evidence of persistence on oral anticoagulants for stroke prevention in non-valvular atrial fibrillation: a cohort study in UK primary care. BMJ Open. 2016 Sep 26;6(9):e011471.
23. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146(12):857–867.
24. Jacobson A. Is there a role for warfarin anymore? (in eng), Hematology Am Soc Hematol Educ Program. 2012;20121:541–546.
25. Holbrook A, Schulman S, Witt DM, *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):e152S–e184S.
26. Stafford DW. The vitamin K cycle. J Thromb Haemost. 2005 Aug;3 (8):1873–1878.

27. Tideman PA, Tirimacco R, St John A, et al. How to manage warfarin therapy. (in eng), Aust Prescr. 2015;382:44–48.
28. Holmes MV, Hunt BJ, Shearer MJ. The role of dietary vitamin K in the management of oral vitamin K antagonists. Blood Rev. 2012 Jan;26(1):1–14.
29. Hughes M, Lip GYH, N. n. c. g. f. m. o. a. f. i. p. on behalf of the Guideline Development Group for the, and c. secondary. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. QJM. 2007;100 (10):599–607.
30. Proietti M, Lane DA. The compelling issue of nonvitamin k antagonist oral anticoagulant adherence in atrial fibrillation patients: a systematic need for new strategies. Thromb Haemost. 2020 Mar;120(3):369–371.
31. Gomes T, Mamdani MM, Holbrook AM, et al. Rates of hemorrhage during warfarin therapy for atrial fibrillation. Cmaj. 2013 Feb 5;185 (2):E121–E127.
32. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213–220.
33. LaMori JC, Mody SH, Gross HJ, *et al*. Burden of comorbidities among patients with atrial fibrillation. Ther Adv Cardiovasc Dis. 2013 Apr;7(2):53–62.
34. Kearon C, Akl EA, Comerota AJ, *et al*. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012 Feb;141(2):e419S–e496S.
35. Herman D, Peternel P, Stegnar M, et al. The influence of sequence variations in factor VII, gamma-glutamyl carboxylase and vitamin K epoxide reductase complex genes on warfarin dose requirement. Thromb Haemost. 2006 May;95(5):782–787.
36. Perzborn E, Roehrig S, Straub A, et al. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Nat Rev Drug Discov. 2011;10(1):61–75.
37. Wong PC, Pinto DJP, Zhang D. Preclinical discovery of apixaban, a direct and orally bioavailable factor Xa inhibitor. (in eng), J Thromb Thrombolysis. 2011;314:478–492.
38. Stacy ZA, Call WB, Hartmann AP, et al. Edoxaban: a comprehensive review of the pharmacology and clinical data for the management of atrial fibrillation and venous thromboembolism. (in eng), Cardiol Ther. 2016;51:1–18.
39. Zhang P, Huang W, Wang L, *et al*. Discovery of betrixaban (PRT054021), N-(5-chloropyridin-2-yl)-2-(4-(N, N-dimethylcarbamimidoyl)benzamido)-5-methoxybenzamide, a highly potent, selective, and orally efficacious factor Xa inhibitor. Bioorg Med Chem Lett. 2009 Apr 15;19(8):2179–2185.
40. Halvorsen S, Ghanima W, Fride Tvete I, *et al*. A nationwide registry study to compare bleeding rates in patients with atrial fibrillation being prescribed oral anticoagulants. Eur Heart J Cardiovasc Pharmacother. 2017;3(1):28–36.
41. Beyer-Westendorf J, Förster K, Pannach S, *et al*. Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry. Blood. 2014;124(6):955–962.
42. Baber U, Mastoris I, Mehran R. Balancing ischaemia and bleeding risks with novel oral anticoagulants. Nat Rev Cardiol. 2014 Dec;11 (12):693–703.
43. Mekaj YH, Mekaj AY, Duci SB, et al. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag. 2015;11:967–977.
44. Douxfils J, Tamigniau A, Chatelain B, et al. Measurement of non-VKA oral anticoagulants versus classic ones: the appropriate use of hemostasis assays. (in eng), Thromb J. 2014;121:24.
45. Wang Y, Bajorek B. New oral anticoagulants in practice: pharmacological and practical considerations. Am J Cardiovasc Drugs. 2014 Jun;14(3):175–189.
46. Hoffman R, Brenner B. The promise of novel direct oral anticoagulants. Best Pract Res Clin Haematol. 2012 Sep;vol. 25(no. 3):351–360.
47. Kubitza D, Becka M, Voith B, et al. Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59–7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther. 2005 Oct;78(4):412–421.
48. Kepplinger J, Barlinn K, Gehrisch S, et al. Abstract T MP57: are The Recommendations For The Emergency Management Of Acute Ischemic Stroke Patients On Novel Oral Anticoagulants Sufficient? Stroke. 2014;45(suppl_1):57.
49. Bauer KA. Pros and cons of new oral anticoagulants. (in eng), Hematology Am Soc Hematol Educ Program. 2013;20131:464–470.
50. Cowell RP. Direct oral anticoagulants: integration into clinical practice. Postgrad Med J. 2014 Sep;90(1067):529–539.
51. Petzold T, Thienel M, Dannenberg L, *et al*. Rivaroxaban Reduces Arterial Thrombosis by Inhibition of FXa-Driven Platelet Activation via Protease Activated Receptor-1. Circ Res. 2020;486(4). 10.1161/CIRCRESAHA.119.315099.
52. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke results from the national registry of atrial fibrillation. JAMA. 2001;285 (22):2864–2870.
53. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk Factor-Based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263–272.
54. Sandhu RK, Bakal JA, Ezekowitz JA, et al. Risk stratification schemes, anticoagulation use and outcomes: the risk–treatment paradox in patients with newly diagnosed non-valvular atrial fibrillation. Heart. 2011;97(24):2046.
55. Hindricks G, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 2020. 10.1093/eurheartj/ehaa612.
56. Lane DA, Lip GYH. Use of the CHA_2DS_2-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation. Circulation. 2012;126(7):860–865.
57. Wu Y. Contact pathway of coagulation and inflammation. (in eng), Thromb J. 2015;131:17.
58. Al-Horani RA, Afosah DK. Recent advances in the discovery and development of factor XI/XIa inhibitors. (in eng), Med Res Rev. 2018;386:1974–2023.
59. Gailani D, Renné T. The intrinsic pathway of coagulation: a target for treating thromboembolic disease? J Thromb Haemost. 2007;5 (6):1106–1112. [Online]. Available: https://liverpool.idm.oclc.org/login?url=https://search.ebscohost.com/login.aspx?direct=true&db=mnh&AN=17388803&site=eds-live&scope=site
60. Babiker RCSMUHM. "Physiology, Coagulation Pathways." StatPearls. [cited 2020 Oct 12]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482253/.
61. Spronk HMH, Padro T, Siland JE, *et al*. Atherothrombosis and thromboembolism: position paper from the second Maastricht consensus conference on thrombosis. Thromb Haemost. 2018;118(2):229–250. (in eng).
62. Weitz JI, 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):130–139.

••• **Phase II clinical trial, comparing osocimab against NOACs in patients at risk of post-operative venous thromboembolism (VTE).**

63. Köhler G, Milstein C. Continuous cultures of fused cells secreting antibody of predefined specificity. Nature. 1975;256(5517):495–497.
64. Koch AW, Schiering N, Melkko S, *et al*. MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans. Blood. 2019;133 (13):1507–1516.
•• **First-in-human Phase I clinical trial for novel antibody MAA868.**
65. Aronora. "XOMA Acquires Royalty Rights to Five Hematology Candidates. [cited 2020 Jan 14]. Available from: http://aronorabio.com/site/xoma-acquires-royalty-rights-to-five-hematology-candidates/.
66. Thomas D, Thelen K, Kraff S, *et al*. BAY 1213790, a fully human IgG1 antibody targeting coagulation factor XIa: first evaluation of safety, pharmacodynamics, and pharmacokinetics. Res Pract Thromb Haemost. 2019;3(2):242–253.
67. Lorentz CU, Verbout NG, Wallisch M, *et al*. Contact activation inhibitor and Factor XI antibody, AB023, produces safe, dose-dependent anticoagulation in a Phase 1 first-in-human trial. Arterioscler Thromb Vasc Biol. 2019 Apr;39(4):799–809.
•• **Important phase 1 first in human trial for antibody Ab023.**
68. Cao H, Biondo M, Lioe H, *et al*. Antibody-mediated inhibition of FXIIa blocks downstream bradykinin generation. J Allergy Clin Immunol. 2018;142(4):1355–1358.
•• **Important early clinical data for FXII inhibiting antibody, CSL312.**
69. U. S. N. L. o. Medicine. "A study to investigate CSL312 in subjects with hereditary angioedema (HAE). [cited 2020 Jul 22]. Available from:https://www.clinicaltrials.gov/ct2/show/NCT03712228.
70. Aronora. "Product Pipeline." [cited 2020 Jul 24]. Available from: http://aronorabio.com/site/pipeline/.
71. Rang HP, Hill RG. Chapter 6 - Choosing the target. In: Hill RG, Rang HP, editors. Drug discovery and development . *Second Edition* ed. London:Churchill Livingstone; 2013. p. 63–76.
72. Bickmann JK, Baglin T, Meijers JCM, et al. Novel targets for anticoagulants lacking bleeding risk. Curr Opin Hematol. 2017 Sep;24 (5):419–426.
73. Ionis. "Ionis earns $75 million from bayer for advancing IONIS-FXIRx and IONIS-FXI-LRx." [cited 2020 Jul 24]. Available from: https://ir.ionispharma.com/static-files/2ecdbe5e-981d-4fab-ba01-16e04a5e3227.
74. Pharmaceuticals I, "Ionis' Factor XI anti-thrombotic medicine advances with Bayer following positive clinical results." 9 October 2019. [Online]. [cited 2020 Jul 26]. Available from: https://ir.ionispharma.com/node/25266/pdf.
75. Veber DF, Johnson SR, Cheng HY, et al. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002 Jun 6;45(12):2615–2623 . (in eng).
76. Arkin MR, Tang Y, Wells JA. Small-molecule inhibitors of protein-protein interactions: progressing toward the reality. (in eng), Chem Biol. 2014;219:1102–1114.
77. Ganellin R, Roberts S, Jefferis R. Introduction to biological and small molecule drug research and development: Theory and case studies. Org Process Res Dev. 2013;17(9):1218. /09/20.
78. Schenone M, Dančík V, Wagner BK, et al. Target identification and mechanism of action in chemical biology and drug discovery. (in eng), Nat Chem Biol. 2013;94:232–240.
79. Mohammed BM, Matafonov A, Ivanov I, *et al*. An update on factor XI structure and function. Thromb Res. 2018 Jan;161:94–105. (in eng).
80. Hayward NJ, Goldberg DI, Morrel EM, et al. Abstract 13747: Phase 1a/1b study of EP-7041: a novel, potent, selective, small molecule FXIa inhibitor. Circulation. 2017;136:A13747–A13747. suppl_1.
•• **Phase 1 clinical trial of small molecule FXI inhibitor.**
81. Therapeutics L. https://www.lunactherapeutics.com/(accessed 2020 Novemeber 23, 2020).
82. Verseon, "Precision Oral Anticoagulants (PROACs)." 2020. [Online]. Accessed 28 July 2020. Available: https://www.verseon.com/anticoagulation.html.
83. Sivaraja M, Clemens DM, Sizikov S, *et al*. VE-1902—A direct thrombin inhibitor with reversible covalent mechanism of action shows efficacy with reduced bleeding in rodent models of thrombosis. Thromb Res. 2020;190:112–121.
84. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: an increasing epidemic and public health challenge. Int J Stroke. 2020 Jan;19:1747493019897870. (in eng).
85. Puy C, Tucker EI, Wong ZC, *et al*. Factor XII promotes blood coagulation independent of factor XI in the presence of long-chain polyphosphates. J Thromb Haemost. 2013 Jul;11(7):1341–1352. (in eng).
86. Visser M, van Oerle R, Ten Cate H, *et al*. Plasma kallikrein contributes to coagulation in the absence of Factor XI by activating Factor IX. Arterioscler Thromb Vasc Biol. 2020;40(1):103–111.
87. Noubouossie DF, Henderson MW, Mooberry M, *et al*. Red blood cell microvesicles activate the contact system, leading to factor IX activation via 2 independent pathways. Blood. 2020;135 (10):755–765.
88. Kearney KJ, Butler J, Posada OM, *et al*. Kallikrein directly interacts with and activates Factor IX, resulting in thrombin generation and fibrin formation independent of Factor XI. Proc Natl Acad Sci U S A. 2021 Jan 19;118(3):e2014810118.