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# Factor XI Inhibition fulfilling the optimal expectations for ideal anticoagulation

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**Abstract**

*Introduction:* Thromboembolic diseases are leading cause of mortality accounting for an estimated 1 in 4 deaths all over the world. Anticoagulation remains the mainstay of prevention and treatment of venous thromboembolic disorders. Conventional anticoagulants have been efficiently used over the last decades, but their clinical use encounters safety and convenience issues. To overcome these limitations, research have focused on development of new targets for anticoagulation leading to a relatively new class of drugs, non-vitamin K antagonist oral anticoagulants, specifically targeting activated factor X and thrombin. However, the search for more potent anticoagulant agents with reduced bleeding risk is still continuing.

*Areas covered:* In this review, we provide an overview on emerging investigational anticoagulant drugs targeting factor XI in the coagulation cascade. We review data about the role of intrinsic pathway in thrombosis and haemostasis and the rationale of different pharmacodynamic approaches targeting factor XI.

*Expert opinion:* Recent evidence suggests that the contact pathway plays a significant role in thrombosis by thrombus stabilization and growth without perturbing haemostasis. Factor XI might be a promising drug target to develop highly effective antithrombotic therapy with safety bleeding profile. Most of these investigational agents are in early development phases, only few have reached early phase clinical trials.

**Keywords:** anticoagulation, coagulation cascade, drug discovery, factor XI, haemostasis, investigational drugs, intrinsic pathway, novel anticoagulants, thrombosis.

## 1. Background

Thromboembolic diseases comprising of major arterial thromboses (ischaemic heart disease and ischaemic stroke) and venous thromboembolism (deep venous thrombosis and pulmonary embolism) are the leading cause of mortality accounting for an estimated 1 in 4 deaths all over the world [1]. Atrial fibrillation (AF) is a known major risk factor for acute thromboembolic events leading to debilitating stroke [2].

Anticoagulation remains the mainstay of primary and secondary prevention, as well as treatment of venous thromboembolic disorders. Conventional anticoagulants, i.e. heparins, low molecular weight heparins, vitamin K antagonists (VKA) have been efficiently used over the last decades, but their clinical use encounters safety and convenience issues[3]. To overcome these limitations, extensive research have focused on development of new targets for anticoagulation leading to a relatively new class of drugs, the non-vitamin K antagonist oral anticoagulants (NOACs), specifically targeting activated factor X and thrombin. With the introduction of NOACs the practice of anticoagulation has been revolutionized as these drugs show relative efficacy, safety and convenience compared to VKAs [4]. However the search for the holy grail of anticoagulation: equally efficacious anticoagulant agents with increased safety profile is still continuing [5].

Current research is focusing on understanding the role of intrinsic pathway (i.e. factor XI and XII) in coagulation processes and investigating their potential as new drug targets to achieve safer anticoagulation. With recent evidence suggesting that the contact pathway may play significant role in thrombosis by thrombus stabilization and growth, the focus has shifted to

develop drugs targeting factors XI and XII. Further larger trials are needed to confirm the additional clinical benefits and optimise treatment strategies.

## 2. Medical need

Anticoagulation is essential for prevention and in the treatment of DVT and PE, and has further expanded to cover peri-operative thrombosis prevention resulting in significant reductions in postoperative morbidity and mortality [6]. AF confers a five-fold increase risk of stroke compared with normal sinus rhythm, with AF-related stroke more likely to be fatal or severely disabling. Thus, stroke prevention is the cornerstone of the management of patients with AF, and risk stratification aids decision-making for thromboprophylaxis [7].

Despite impressive progress in drug development over the last decade, anticoagulation remains challenging for the clinician with the aim to achieve safety thrombosis prevention balanced by the potential complications and risk of bleeding. Accordingly agents with optimized efficacy- safety profile are needed. The requirements of new antithrombotic agents are summarized in Table 1.

## 3. Limitations of existing treatment

Heparins were discovered almost a century ago and followed by coumarins have been the gold-standard of anticoagulation pharmacy for the past 60 years; however, their limitations (including unpredictable interindividual response, narrow therapeutic range, frequent monitoring, high potential for food and drug interactions) led to development of novel agents targeting the coagulation cascade [8].

As NOACs have proved to offer relative efficacy, safety, and convenience compared with VKAs in the prevention of stroke and VTE, they are increasingly used as alternatives to

VKAs [4]. However, a significant proportion of AF patients are not prescribed anticoagulants because of bleeding concerns [9]. According to a metaanalysis including all the randomized clinical trials conducted on the four commercially available NOACs, the annual rate of major bleeding is 2% to 3% and the annual rate of intracranial bleeding is 0.3-0.5% in patients with AF [4].

All the NOACs have relatively predictable pharmacokinetic profiles and fixed daily doses without requiring frequent anticoagulation monitoring. Undoubtedly NOACs have less drug interactions compared with VKAs, although some pharmacokinetic interactions with accompanying drugs and comorbidities still need to be considered [10]. Additionally all the NOACs are substrate for the P-glycoprotein transporter, and rivaroxaban and apixaban also metabolized in the liver through the CYP-dependent isozyme pathway (CYP3A4). Thus, competitive inhibition of P-glycoprotein or CYP3A4 pathway will result in increased plasma levels of NOACs. Furthermore, most NOACs have some degree of renal excretion, with the greatest renal dependency for dabigatran; thus, the elimination of NOACs is reduced in patients with impaired renal function, potentially impacting efficacy and increasing bleeding risk. Although the phase III trials excluded patients with severe renal impairment of a creatinine clearance (CrCl) <25-30 ml/min, some cohort studies have demonstrated that NOACs also provide effective thromboprophylaxis in AF patients with mild to moderate renal dysfunction (CrCl of 30-79 ml/min)[11]. Alternative pharmacologic strategies with lower renal dependence are needed and adverse bleeding remains the most important area of improvement.

## 4. Scientific rationale and current research goals

The classical two distinct pathways of the blood coagulation cascade include the extrinsic pathway, initiated by tissue factor and further FVIIa driven activation of FX; intrinsic pathway where activation of FX is propagated by FIXa and FVIIIa. With a more precise biochemical understanding of the coagulation processes, it is evident now that the extrinsic pathway is responsible for initiation and activation of the coagulation processes as a response to vascular injury; however, the role of intrinsic pathway in haemostasis is secondary [12].

However the focus has been shifted to elucidate the biological role of the contact system, which might be a critical proinflammatory and prothrombotic mediator by activating intrinsic pathway. Also named as plasma kallikrein-kinin system, the contact system comprises of three serine proteases, coagulation factors XI and XII and plasma prekallikrein and the nonenzymatic cofactor, high molecular weight kininogen [13]. . The only activators of the contact system were thought to be the artificial sites and extracorporeal conditions for decades. Recent evidence suggests that negative charge macromolecules such as RNA, DNA derived from injured cells or activated neutrophils as well as polyphosphates derived from activated platelets are potential triggers of the contact system, acting as a distinct initiationof coagulation at the site of vascular injury in thrombo-inflammatory disorders [14][15][16][17]. While long chain polyphosphates indeed have been shown to activate the contact pathway, a few of the other triggers, such as short chain polyphosphates and neutrophil extracellular traps, are cofactors rather than triggers. In fact, the recent report by the Morrissey group revealed that the purification protocol used by several of the cited studies might have created an artefact in the measurement of activation of FXII,

observing that the purification columns used in the studies contained silica (a potent activator of FXII) [18]. These trigger mechanisms need further clarification.

Factor XI is a central player in thrombin generation in the amplification phase and may lead to overproduction of thrombin with excessive clots formation resulting in pathologic thrombosis [19]. Therefore factor XI would be a favourable antithrombotic drug target without major impact on haemostasis as the selective inhibition of this enzyme would leave the extrinsic and common pathways of coagulation intact. This concept is supported by emerging research on different experimental thrombosis models (factor XI, XII deficient mice) proving that the contact system is essential for thrombus stabilization and growth, whereas haemostasis is not affected [20][21].

Current epidemiologic and clinical data show that human deficiency of FXI (haemophilia C) rarely causes spontaneous bleeding [22][23] and patients known with that congenital disorder are protected from VTE and ischaemic stroke [24]. Likewise, those with elevated levels of FXI are more prone to thromboembolic events, and the levels of FXI correlate with stroke risk in female patients on hormonal contraceptive medication [22][25]. Factor XI deficient patients rarely bleed spontaneously but do bleed after haemostatic challenge such as tooth extraction. Data on the role of FXII in thrombosis are more conflicting, as patients with partial or severe FXII deficiency are not protected from thromboembolic diseases; however data are limited due to the rare occurrence of the disease [26][22].

According to epidemiological data, only factor XI deficiency is associated with bleeding phenotype in humans, whereas factor XII, PK and HK deficiencies are not associated with

impaired haemostasis, not even in case of major surgery. However the *in vitro* clotting defect is evident, as surface activation to FXII assays measuring the activity of intrinsic and common pathways resulted in prolonged activated partial thromboplastin time [27]. These fundamental findings suggest that factor XI and XII are playing different roles in "pathologic" thrombosis and "physiologic" haemostasis, leading research to develop specific inhibitory drugs as potential anticoagulants with the lack of bleeding risk.

## 5. Competitive environment: a review of drugs in early development phases

Current investigational drugs specifically targeting factor XI can be divided in three categories based on the innovative pharmacodynamic strategies used in the process of drug development: Antisense oligonucleotides (ASO), Monoclonal antibodies (MAb) and aptamers or small molecules.

ASO act by reducing the hepatic synthesis of the clotting protein through a specific binding to the complementary mRNA target and causing catalytic degradation. MAb are parenterally administered molecules with a quick onset and slow offset of action, specifically binding to factor XI or factor XIa and counteracting theactivation or the effect of the protein [28][29]. A potential advantage of these new class of drugs for clinical use could be the prolonged half-life, making possible a once monthly subcutaneous administration; however, in case of severe bleeding the reversal of the effect would be problematic unless a specific reversal agent was available. A third class of drugs targeting factor XI are orally administered aptamers or small molecules with rapid onset and offset of action, blocking the active site or inducing allosteric modulation of the protein. Another indirect approach is to inhibit the stimulators of contact pathway activation, neutralizing nucleic acids or polyphosphates [30].

1. **ASO targeting the intrinsic pathway**

These have been successfully investigated in several animal venous and arterial thrombosis models and proved to have potent thromboprophylactic effects with lowered bleeding risk compared to warfarin and enoxaparin [29].

In a baboon thrombosis model, FXI ASO reduced FXI levels in a time- and dose-dependent manner and did not prolong the bleeding time, furthermore demonstrating protection from contact-pathway initiated thrombus propagation [31]. The safety and tolerability of FXI ASO therapy was evaluated in cynomologous monkeys and in a phase I double-blind study involving healthy volunteers [32][33].

A promising drug candidate, IONIS-FXI-RX (formerly ISIS-416858), discovered and developed by scientists at Ionis Pharmaceuticals, was the first agent tested in humans for the prevention of thromboembolic events in patients undergoing orthopaedic surgery [34]. In this open-label phase II study 300 elective patients undergoing total knee arthroplasty were involved and IONIS-416858 proved to be safe and effective compared to standard thromboprophylaxis with enoxaparin. Currently, IONIS- 416858 is undergoing phase II clinical testing, evaluating the safety, tolerability, PK and PD in patients with end-stage renal disease on haemodialysis (NCT02553889).

2. **MAbs targeting factor XI**

MAbs are antibodies designed and produced by complex biotechnological processes using a single clone of B cells and specifically targeting a particular antigen. Since the hybridoma

technique has been introduced (making it possible to obtain pure MAbs in large amounts) the clinical innovative therapeutic use of MAbs has been largely enhanced [35]. These agents are specifically binding to the coagulation protein and counteracting its activation or activity.

Aronora Inc has developed an antibody aimed to precisely target the A2 domain of FXI, acquiring a different mechanism of action compared to the synthetic small molecules or the antibodies targeting the active site of FXIa. This MAb does not inhibit the activity of FXIa, it only prevents the activation of FXI by FXIIa, but not by thrombin. Withpromising results in preclinical studies [36][37], AB023 (Xisomab 3G3) has entered clinical trials. After completion of phase 1 clinical trial (NCT03097341), the drug has been progressed to a Phase 2 study (NCT03612856) in order to evaluate the safety and efficacy profile in patients with end stage renal disease on chronic hemodialysis.

Another potential MAb drug candidate, a fully humanized IgG4 FXIa antibody, developed by Bayer (BAY-1213790) is currently being tested as a thromboprophylactic drug, and compared to enoxaparin and apixaban in patients who have undergone knee replacement surgery (NCT03276143).

## 3. **Synthetic small molecules**

These promising agents target the active site of factor XI and are proved to be effective in rabbit and rat models [25]. Factor XI is a polypeptide molecule with a dimeric structure, comprising of a trypsin-like catalytic domain and 4 apple domains, that make it similar to prekallikrein, however with distinguishing features on apple 3 domain, which promotes the interaction with thrombin generation mechanism. Due to the structural molecular similarities that the trypsin-like catalytic domain shares with those characterizing other coagulation factors, it is essential in the process of drug design to pinpoint a molecule that is highly selective for factor XI and does not bind to other domains [38].

Such a target seems to be reached by an investigational factor XI inhibitor molecule, BMS-262084, synthesized by Bristol-Mayers Squibb. BMS-262084 is a monocyclic 4-carboxy-2-azetidinone containing, mechanism-based inactivator of the active-site of human factor XIa. This is known to exert an irreversible inhibition over factor XIa by acting through the formation of a covalent bond with the active site serine residue with a strong potency of inhibiting this specific step in the coagulation cascade (the half maximal inhibitory concentration, $IC_{50}$ of 2.8 nM) [39]. Antithrombotic and haemostatic effects were tested in in- vivo rat models and BMS-262084 proved to be highly selective compared to other coagulation proteases. Furthermore, it has been proved to be more specific for human FXIa with respect to the other human serine proteases involved in the coagulation process, namely FXa, FIXa, FVIIa, FXIIa, plasma kallikrein and to factors involved in the fibrinolytic process (such as tissue plasminogen activator, urokinase and plasmin)with a specificity of 12000 fold over FXa and 3800 fold over thrombin [40].

In an ex-vivo model BMS-262084 was studied together with apixaban and rivaroxaban, known FXa inhibitors [41]. Activated factor X inhibitors completely blocked tissue factor-dependent platelet aggregation at a concentration of 1,000 nM, whereas the studied activated factor XI inhibitor molecule did not affect tissue factor-induced platelet aggregation even at concentrations up to 10 μM. However, the same drug doubled the activated thromboplastin time at a concentration of 0.14 μM [39], hence such behaviour may not be attributed to insufficient concentration. It is conceivable that antithrombotic effect driven by FXI inhibition may not be safe under-conditions where tissue factor is driving thrombosis.

Other synthetic molecules with various chemical structures proved to be effective in inhibiting

FXI active site, either with an acyclic, monocyclic or bicyclic structure. As a representative of phenylimidazoles, also known as BMS-724296 is a molecule synthesized at Bristol-Mayers Squibb that contains a S)-2-phenyl-1-(4-phenyl-1H- imidazol-2-yl) ethanamine core and has a Ki = 0.3 nM with respect to FXI [42]. This molecule has proved antithrombotic effects in a rabbit AV-shunt thrombosis model. It showed Ki = 5 nM with respect to plasma kallikrein and Ki = 23 nM to trypsin, however a specificity of 10000+ fold over FXa, FVIIa, FXIIa, FIXa, thrombin, and chymotrypsin has been observed. Whilst exerting its antithrombotic effect doubles the aPTT at a concentration of 1 μM whereas the prothrombin time is doubled at 40 μM.

The a-ketothiazole arginine derivatives are tripeptidomimetic FXIa inhibitors, with a α-ketothiazole moiety as a C-terminal group that exerts an irreversible inhibitory function over FXI by covalently binding a residue (Ser195) in its active site. Such molecules are proved to be effective in in vivo models showing clot size reduction without causing significant collateral effects and without prolonging clotting time [43]. The IC50 value of the most potent inhibitor of this class is 6 nM. APTT was doubled up by this compound at a concentration of 2.4 μM whereas a two-fold increase in Prothrombin time was registered at 25 μM. Efficacy against venous thrombosis has been proven in a rat model with a dosage of 0.25 mg/kg.

Tetrahydroquinoline derivatives are small bicyclic molecules acting as reversible FXI active site inhibitor. The most potent molecule of this class showed a FXIa Ki = 0.2 nM. It is specific towards FXIa with a selectivity about 1000 folds higher when compared to other enzymes; nonetheless, it is less sensitive when it comes to kallikrein (23 fold) and activated protein C (365 fold). In-vitro aPTT shows EC2x of 2.2 μM, therefore it is conceivable that plays a role in the

intrinsic coagulation system, whereas it does not affect the prothrombin time with IC2x > 20 μM [44].

After showing promising early results in preclinical studies, a first small molecule drug candidate, BMS 986177, has recently been advanced into clinical Phase II testing in patients with end-stage renal disease on chronic stable hemodyalisis (NCT03000673). For more details about experimental drugs targeting the contact pathway, see table 2.

## 6. Potential development issues

Some vulnerable patient groups: very elderly, with malignant co-morbidities and advanced renal failure still remain an area of concern regarding anticoagulation, given that those patient populations were excluded from randomized controlled trials of currently available NOACs, therefore future new anticoagulants would address this unmet clinical need.

Factor XI directed strategies are being tested as thrombosis preventive agents, a further stage of development would be to assess their effects and potentials in the treatment of established venous or arterial thrombotic disorders.

These agents are compounds from heterogeneous chemical classes with different pharmacokinetics and pharmacodynamics which may attribute some potential clinical advantages to be considered in further drug development. The quick onset of action of MAbs the associated long half- lives and subcutaneous administration might be more suitable forchronic indications, like secondary prevention after unprovoked VTE or prevention of stroke in patients with AF and associated severe or end-stage kidney disease. Providing reduced frequency of

administration (weekly or monthly regimens) may serve as clinical benefit with favourable impact on medication adherence. However, in case of severe bleeding the slow offset of action could be an issue, unless a reversal agent was concomitantly developed. Considering their advantages of specificity, efficacy, and safety, there is now widespread acceptance of mAbs as innovative therapeutic agents. Furthermore the associated risks of immunogenicity with biopharmaceutical products warrants further detailed assessment in the drug development process.

The quick onset and offset of actions of orally administered aptamers or small molecules, blocking the active site of the activated FXI may offer advantages in acute settings. One of the most important indications for their use could be anticoagulation in patients on haemodialysis or patients deemed at high bleeding risk, both of them representing an unmet clinical need.

## 7. Conclusion

Bleeding complications are still causing concerns in the clinical use of current anticoagulants and certain vulnerable patient populations are still not safely prescribed in spite of the increasing armamentarium of new anticoagulants. With recent evidence suggesting that the contact pathway may play significant role in thrombosis by thrombus stabilization and growth, the focus has shifted to develop drugs targeting factor XI [45].

The novel pharmacologic strategies, which aim to specifically target factor XI so far, are as follows: (i) ASO; (ii) MAb; both strategies are aimed to act by blocking the activation or activity of the clotting factor, and are parenterally administered with a quick onset of action; and (iii) aptamers and small molecules block the active site or induce allosteric modulation of the protein [29][28].

Most of these investigational agents are in early discovery and development phases, and only one have reached early phase clinical trials. IONIS-416858 was tested and proved to be safe and effective in thromboprophylaxis after orthopaedic surgery; and currently, IONIS-416858 is undergoing phase II clinical testing in patients with end-stage renal disease on hemodialysis.

Antisense oligonucleotides and monoclonal antibodies targeting factor XI are widely investigated in experimental models with proven thromboprophylactic effects. Nevertheless, further investigations are compulsory to prove their safety and efficacy of inhibiting the intrinsic system in humans and to establish which particular pharmacotherapeutic option is best to be targeted for further development [45]. As summarised in this review, novel therapeutics targeting activated factor XI might fulfil the criteria of being the "holy grail", being an effective anticoagulant without any excess of bleeding compared to no antithrombotic therapy.

## 8. Expert opinion

Current research is focusing on understanding the biological role of the contact system, a critical proinflammatory and prothrombotic mediator activating the intrinsic pathway and investigating factor XI as a potential new drug target to achieve safer anticoagulation.

The requirements of an "ideal" anticoagulant are numerous with the main objective to attenuate thrombosis without perturbing haemostasis. The main focus in drug development so far was to generate a very efficient pharmacodynamic profile, however some other important requirements, like stable and predictable pharmacokinetics, lack of side effects and toxicity, fast onset and offset of action, availability of reversal agent, low potential for food or drug interactions, fixed

dosing without anticoagulation monitoring and lower renal dependence should be taken into consideration.

After recent advances in structural and molecular biology, monoclonal antibodies and antisense oligonucleotides are attracting interest in drug development for various pathologies. Their unique pharmacodynamic profile with slow onset of action and prolonged half-life may be of benefit in chronic indications for anticoagulation. ASOs targeting factor XI have proved to have excellent safety profile in early clinical trials, making them attractive for further testing in patient with high bleeding risks.

Various innovative pharmacodynamic approaches have been developed and tested in animal models. However, most of these investigational agents are in early discovery and development phases, only few have reached early phase clinical trials. Further studies are needed to confirm the potential clinical benefits and optimise treatment strategies.

With recent evidence suggesting that the contact pathway plays significant role in thrombosis by thrombus stabilization and growth without perturbing hemostasis, factor XI might be a promising drug target to develop highly effective antithrombotic therapy with safer bleeding profile.

**All figures and tables in this article are original and have not been published before.**

Table 1. Requirements of new antithrombotic agents

| |
|---|
| At least as effective as NOACs |

| |
|---|
| Predictable response, stable pharmacokinetics |
| Low potential for food or drug interactions |
| Fast onset and offset of action |
| Wide therapeutic range |
| Oral fixed dose, no need for routine anticoagulation monitoring |
| Low incidence and severity of adverse effects and bleeding |
| Availability of reversal agent |
| Lower renal dependence |
| Cost-effective |



**Table 2. Experimental drugs targeting factor XI**

| Compound | Company | Structure | Indication | Stage of development | Mechanism of action |
|---|---|---|---|---|---|
| BMS-262084 | Bristol-Mayers Squibb | Monocyclic 4-carboxy-2-azetidinone | Antithrombotic | Pre-clinical studies | Inactivator of the active-site of human FXIa |
| BMS-724296 | Bristol-Mayers Squibb | Phenylimidazoles | Antithrombotic | Pre-clinical studies | Reversible binding to the active site of FXIa |
| 14E11 | N/A | Monoclonal antibody | Animal thrombosis models: mouse carotid artery thrombosis model; baboon arteriovenous | Pre-clinical studies<br>Prevention of artery occlusion; reduced platelet rich thrombus growth and | Specific binding and blocking FXI activation by FXIIa |

| | | | | | |
|---|---|---|---|---|---|
| | | | shunt model Cheng et al, 2010 [36] | fibrin deposition in collagen-coated grafts | |
| Xisomab* (AB022)<br><br>humanized version of 14E11 | Aronora Inc., NCT03097341 | Monoclonal antibody | Antithrombotic | Ongoing Phase I clinical trial<br><br>Open label, single ascending dose, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK and PD in healthy adult subjects | Specific binding and blocking FXI activation by FXIIa |
| BAY 1213790* | Bayer Healthcare, NCT03276143 | Fully humanized IgG4 antibody | VTE prophylaxis in knee arthroplasty, n= 700 | Ongoing Phase II clinical trial<br><br>FOXTROT study<br><br>BAY 1213790 compared to apixaban and enoxaparin | Specific binding to active site of FXIa and blocking FXIa activity |
| O1A6 | N/A | Monoclonal antibody | Primate thrombosis model<br><br>O1A6 2 mg/kg vs. aspirin 32 mg/kg for graft occlusion prevention; Tucker et al, 2009 [37] | Pre-clinical studies<br><br>99% inhibition of plasma FXIa activity, suppressed thrombin-antithrombin complex formation, inhibited platelet and fibrin deposition; O1A6 prevented the occlusion of smaller-diameter grafts without affecting bleeding times | Specific binding to FXI and blocking activation or activity |
| Factor XI ASOs | N/A | Antisense oligonucleotides | Catheter thrombosis model in rabbit; Yau et al, 2014 [46] | Pre-clinical<br><br>Catheter occlusion time increased (2.3 fold) | Reducing the hepatic synthesis of FXI |
| | N/A | Antisense | Baboon model of thrombosis and | Pre- clinical | Reducing the hepatic |

| | | | | | |
|---|---|---|---|---|---|
| | | oligonucleotides | hemostasis; Crosby et al, 2013 [31] | ASO mediated reduction of FXI plasma level ≥50% resulted in sustainable antithrombotic effect, without increased risk of bleeding | synthesis of FXI |
| IONIS-416858* | Ionis Pharmaceuticals | Antisense oligonucleotides | VTE prophylaxis after knee arthroplasty, n=300<br><br>FXI- ASO 200 mg or 300 mg vs. enoxaparin 40 mg Buller et al, 2015 [34] | Phase II clinical trial Noninferiority for the 200 mg group, superiority for the 300 mg group compared to enoxaparin ($p<0.001$ for both); Lower bleeding rates for FXI- ASO groups (3% vs. 8%) | Reducing the hepatic synthesis of FXI |
| | Ionis Pharmaceuticals, NCT02553889 | Antisense oligonucleotides | Anticoagulation in patient with ESRD on hemodialysis<br><br>Randomized, double blind, placebo controlled study | Phase II clinical trial<br><br>No results published yet | Reducing the hepatic synthesis of FXI |

*Investigational drugs advanced into clinical trials

ASO- antisense oligonucleotides; aPTT- activated prothrombin time; ESRD- end-stage renal disease; FXI- Factor XI; MAb- monoclonal antibody; PD- pharmacodynamics; PK- pharmacokinetics; VTE- venous thromboembolism.



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