

# Factor XI Inhibition for the Prevention of Venous Thromboembolism: An Update on Current Evidence and Future perspectives

Geraldine Poenou <sup>1</sup>, Teona Dumitru Dumitru <sup>1-3</sup>, Ludovic Lafaie<sup>4,5</sup>, Valentine Mismetti<sup>5,6</sup>, Marco Heestermans <sup>5,7</sup>, Laurent Bertoletti <sup>1,5,8</sup>

<sup>1</sup>Therapeutic and Vascular Medicine Department, University Hospital of Saint Etienne, Saint Etienne, France; <sup>2</sup>Internal Medicine Department, University Hospital Santa Lucia, Cartagena, Murcia, Spain; <sup>3</sup>Catholic University San Antonio, Murcia, Spain; <sup>4</sup>Geriatric Department, University Hospital of Saint Etienne, Saint Etienne, France; <sup>5</sup>INSERM, UMR1059, Haemostasis and Vascular Dysfunction Team, Jean Monnet University, Saint-Etienne, F-42055, France; <sup>6</sup>Pneumology Department, University Hospital of Saint Etienne, Saint Etienne, France; <sup>7</sup>Auvergne-Rhône-Alpes French Blood Donation Agency, Saint-Etienne, F-42100, France; <sup>8</sup>INSERM, CIC-1408, University Hospital of Saint Etienne, Saint Etienne, France

Correspondence: Laurent Bertoletti, Therapeutic and Vascular Medicine Department, University Hospital of Saint Etienne, Saint Etienne, France, Tel +33477827771, Fax +33477820482, Email Laurent.bertoletti@gmail.com

**Abstract:** During the past decade, emergence of direct oral anticoagulants (DOACs) has drastically improved the prevention of thrombosis. However, several unmet needs prevail in the field of thrombosis prevention, even in the DOACs' era. The use of DOACs is still constrained and the drugs cannot be administered in every clinical scenario, such as an increased anticoagulant-associated bleeding risk, particularly in some specific populations (cancer – notably those with gastrointestinal or genitourinary cancer – and frail patients), the impossibility to be used in certain patients (eg, end-stage kidney failure during hemodialysis, pregnancy and breastfeeding), and their lack of efficacy in certain clinical scenarios (eg, mechanical heart valves, triple-positive antiphospholipid syndrome). Efforts to find a factor that upon antagonization prevents thrombosis but spares haemostasis have resulted in the identification of coagulation factor XI (FXI) as a therapeutic target. After briefly recapitulating the role of factor XI in the balance of haemostasis, we propose a narrative review of the key data published to date with compounds targeting factor XI to prevent thrombosis as well as the main ongoing clinical studies, opening up prospects for improving the care of patients requiring thrombosis prevention.

**Keywords:** FXI inhibitor, venous thromboembolic events, thromboprophylaxis, anticoagulant, clinical trials

## Introduction

During the past decade, emergence of direct oral anticoagulants like rivaroxaban, apixaban and edoxaban (DOACs) has drastically improved the prevention of thrombosis.<sup>1</sup> DOACs were found to be as efficient as conventional therapy in the prevention of recurrent venous thrombotic events, while they were associated with a decreased risk of major bleeding. Alongside with low-molecular weight heparin (LMWH) or fondaparinux, DOACs has become a new option in VTE prevention for total knee or hip replacements. To prevent thromboembolic events in patients with non-valvular atrial fibrillation (AF), DOACs have demonstrated their efficacy and safety as compared to vitamin-K antagonists (VKAs). Hence, DOACs are currently recommended as the main option of therapy in most situations with an indication of anticoagulant therapy,<sup>2-4</sup> and they have replaced VKAs in the majority of patients with VTE<sup>5</sup> or AF.<sup>6</sup>

However, many unmet needs prevail in the field of thrombosis prevention, even in the DOACs' era.<sup>7</sup> The use of DOACs is still constrained. In increased anticoagulant-associated bleeding risk population (such as cancer – in particularly those with gastrointestinal or genitourinary cancer – and frail patients), DOACs cannot be administered. Moreover, in certain patients DOACs use is either not recommended nor even impossible (eg end-stage kidney failure, pregnancy and breastfeeding) or either inefficient (eg mechanical heart valves, triple-positive antiphospholipid syndrome).<sup>8-13</sup> Therefore, there is still a need for new and improved anticoagulant drugs. All the current anticoagulants

antagonize activated factor X (FXa) and/or thrombin function, either directly or indirectly. These two proteases play an essential role for haemostasis and therefore administration of current anticoagulants coincide with an increased risk of bleeding. Efforts to find a factor that upon antagonization prevents thrombosis but spares haemostasis have resulted in the identification of coagulation factor XI (FXI) as a therapeutic target.<sup>14</sup>

After briefly recapitulating the role of factor XI in the balance of haemostasis, we propose a narrative review of the key data published to date with compounds targeting factor XI to prevent thrombosis as well as the main ongoing clinical studies, opening up prospects for improving the care of patients requiring thrombosis prevention.

## Factor XI in the Coagulation Cascade: The Perfect Target?

In the traditional representation of the coagulation cascade, comprised of the intrinsic, extrinsic, and the common pathway, FXI is placed in the intrinsic “arm” or contact activation pathway of coagulation.<sup>15,16</sup> FXI was not considered as a serious therapeutic target to prevent thrombosis, since its deficiency only causes a mild bleeding phenotype (hemophilia C). This means that antagonizing the coagulation factor would be safe without severe bleeding as a side effect, but thrombosis prevention would not be as effective as traditional anticoagulants such as LMWHs or heparin. In humans, deficiencies for contact activation proteins (coagulation factor XII (FXII), prekallikrein (PK), and high-molecular-weight kininogen) do not coincide with a bleeding phenotype.<sup>17,18</sup> For this reason, contact activation was long regarded as irrelevant for human thrombosis, although direct activation of FXII using an artificial negatively charged surface leads to clotting of plasma. Based on that principle, the APTT (activated partial thromboplastin time) test measures plasma clotting time upon activation of FXII using an artificial contact activator such as silica or ellagic acid, and the relatively simple procedure of the test allows a physician to detect abnormalities regarding the plasma levels of certain coagulation factors.<sup>19</sup> FXI was not considered as a serious therapeutic target to prevent thrombosis, since its deficiency only causes a mild bleeding phenotype (hemophilia C).<sup>20</sup> This means that antagonizing the coagulation factor would be safe without severe bleeding as a side effect, but thrombosis prevention would not be as effective as traditional anticoagulants such as LMWHs or heparin.

Recently, the interest for FXI has increased dramatically, since it has been suggested that FXI is more important for thrombosis than for hemostasis. This would make FXI an ideal target to prevent venous thrombosis while minimizing the risk for (severe) bleeding (Figure 1). Using a thrombosis mouse model it was shown that FXII and FXI deficient mice are resistant to thrombosis.<sup>21</sup> Interestingly, deficiency in either of these factors did not coincide with bleeding. Accordingly, using compounds that antagonize FXI function, such as antisense oligonucleotides<sup>22</sup> or blocking antibodies,<sup>23,24</sup> thrombosis was reduced in preclinical animal models. In recent years, several contact activators involved in venous thrombosis onset have been proposed to serve as physiological FXII activators, such as DNA,<sup>25</sup> RNA,<sup>26</sup> platelet

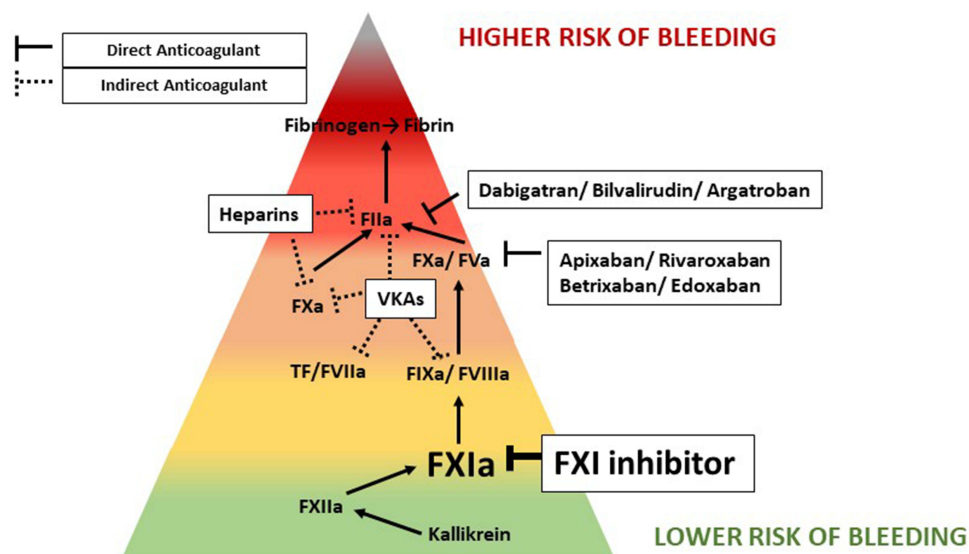


Figure 1 Anticoagulant associated bleeding risk.

polyphosphates,<sup>27</sup> and misfolded proteins.<sup>28</sup> Based on the data from these preclinical studies, FXI could be regarded to serve as a substrate exclusively of FXIIa and thus only involved in coagulation as a consequence of contact activation. However, this does not translate to the human situation in which FXI deficiency, unlike FXII and PK, coincides with a bleeding phenotype and, unlike for FXI plasma levels, FXII and PK levels do not appear to be correlated with risk of VTE.<sup>29</sup> This discrepancy is most likely explained by the discovery that FXI is also activated by thrombin, the key mediator of coagulation.<sup>30</sup> This means that upon thrombin formation coagulation can be maintained via a positive feedback loop by thrombin-mediated activation of FXI. The extent to which the proteases FXIIa and thrombin contribute to FXI activation in humans is not entirely clear and most likely depends on the specific biological circumstances.

The reason why FXI seems to be pivotal in separating hemostasis from thrombosis could be found in the availability of the major driver to start coagulation, tissue factor (TF). When hemostasis needs to be restored, usually in the case of a vascular injury, large quantities of extravascular TF are exposed to the circulation. Substantial TF exposure and according FVIIa formation cause a rapid propagation of coagulation leading to fibrin formation mediated by the dominant extrinsic pathway. In contrast, thrombosis is usually not caused by vascular injury but by a more modest trigger, for instance upon exposure of the circulation to compounds associated with endothelial cells, such as TF+ monocytes,<sup>31</sup> microvesicles,<sup>32</sup> neutrophil extracellular traps,<sup>33</sup> or platelet polyphosphates.<sup>27</sup> As a consequence, the initial burst of thrombin formation is significantly lower and for that reason feedback mechanisms, including thrombin-mediated FXI activation, to maintain a steady flow of freshly generated thrombin may play a more significant role. When coagulation is initiated by the introduction of an artificial contact activation surface, such as placement of a central venous catheter<sup>34</sup> or extracorporeal membrane oxygenation (ECMO)<sup>35</sup> treatment, it is not difficult to envision the benefit of FXI inhibition to reduce thrombosis risk while sparing the patient from (severe) bleeding.

## Targeting Factor XI in Patients: What Do We Currently Know?

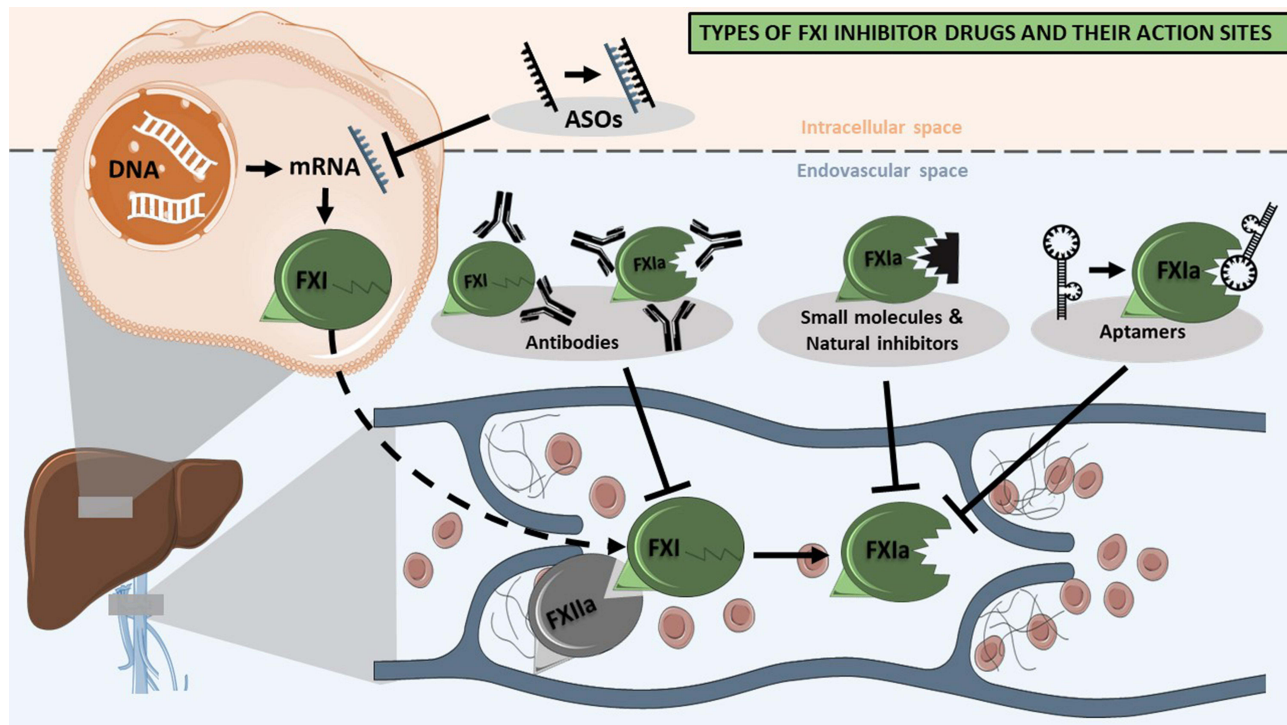
Several therapeutic approaches to target the FXI protein in humans have been proposed, including the use of antisense oligonucleotides (ASOs), aptamers, monoclonal antibodies, natural peptide inhibitors, and synthetic small peptidomimetic molecules (Figure 2). The main pharmacological characteristics of each type of drugs are summarized in Table 1. Natural inhibitors, such as Ir-CPI, seem to be the least feasible option to use as a therapeutic due to their slow on- and offset, and the relatively high risk of negative side effects.<sup>36</sup> Small peptidomimetic molecules, such as Milvexian/BMS-986177 or BAY 2433334, are currently the only class of drugs that can be delivered orally. They have a short half-life and a renal clearance similar to DOACs.<sup>37,38</sup> In contrast, ASOs (such as Factor XI LICA, IONIS FXI-LRx/ISIS 416858) and monoclonal antibodies (such as Xisomab 3G3/AB023, Osocimab/BAY1213790 or Abelacimab/MAA868) have longer half-lives for up to 30 days, which enables a decreased frequency of administration and thus may increase the patient adherence and compliance.<sup>39–41</sup> Antibodies and ASOs approaches to target FXI differ in their onset of action; upon administration, monoclonal antibodies lower FXI function after hours, while the effect of ASOs only becomes apparent after several weeks. Most likely for this reason, inhibition of FXI using monoclonal antibodies are currently more explored.

Several FXI inhibitors are being developed and tested on humans. Published Phase I trials do not report any safety concerns for FXI drugs (Table 2).

Completed Phase II trials exist with ASOs, monoclonal antibodies, and small molecules (Table 3). There are no published data regarding the use of natural inhibitors in clinical trials. The vast majority of patients included in phase II trials to assess anti-FXI therapy in prevention of VTE were patients undergoing total knee replacements.

In the FXI-ASO TKA study,<sup>42</sup> Büller et al randomised 300 patients undergoing total knee arthroplasty to receive one of two doses of an ASO against FXI (IONIS FXI-LRx 200 mg or 300 mg) or 40 mg of enoxaparin once daily. The primary efficacy outcome was a composite of objectively documented symptomatic VTE or asymptomatic DVT. The principal safety outcome was clinically relevant bleeding, a composite of major and clinically relevant non-major bleeding, up to day 30 after surgery. All the events of interest were adjudicated by an independent adjudication committee, blinded to the treatment arm. At 200-mg, FXI-ASO was non-inferior (27%), while the 300-mg was superior (4%) to enoxaparin (30%) ( $P < 0.001$ ). Rates of bleeding were inferior in the FXI-ASO groups (both 3%) than in the enoxaparin group (8%).

The ANT-005 TKA<sup>43</sup> study was a non-inferiority phase II trial, comparing the post-operative admission of 3 unique doses of the FXIa antibody abelacimab (30, 75, or 150 mg), to one daily subcutaneous enoxaparin (40 mg) in patients undergoing total knee arthroplasty. The primary outcome was a composite of objectively documented symptomatic VTE



**Figure 2** Types of FXI inhibitor drugs and their action sites.

or asymptomatic DVT (on systematic venography realized between day 8 to 12). The principal safety outcome was clinically relevant bleeding, a composite of major and clinically relevant non-major bleeding, up to day 30 after surgery. All the events of interest were adjudicated by an independent adjudication committee, blinded to the treatment arm. Abelacimab (at the two highest doses) was significantly non-inferior to enoxaparin, in terms of rates of VTE (4% and 5%, compared with 22% with enoxaparin).

In the FOXTROT Randomized Clinical Trial,<sup>41</sup> investigators randomized 813 patients to receive either single intravenous Osocimab postoperative doses of 0.3 mg/kg (n = 107), 0.6 mg/kg (n = 65), 1.2 mg/kg (n = 108), or 1.8 mg/kg (n = 106); preoperative doses of 0.3 mg/kg (n = 109) or 1.8 mg/kg (n = 108); or 40 mg of subcutaneous enoxaparin once daily (n = 105) or 2.5 mg of oral apixaban twice daily (n = 105) for at least 10 days (or until venography) after knee arthroplasty. The primary efficacy outcome was venous thromboembolism (assessed by mandatory bilateral venography performed 10 to 13 days after surgery or confirmed symptomatic deep vein thrombosis or pulmonary embolism). The primary safety outcome was a composite of major or clinically relevant nonmajor bleeding, assessed until 10 to 13 days postoperatively. Of note, only 600 of the 813 randomized patients were included in the per-protocol analysis. Only preoperative dose of 1.8 mg/kg was found to be superior to enoxaparin (risk difference of 15.1%; 2-sided 90% CI, 4.9% to 25.2%). No regimen of Osocimab was found to be superior to apixaban.

The AXIOMATIC-TKR<sup>44</sup> study assessed the efficacy and safety of the oral FXIa inhibitor Milvexian, in patients undergoing total knee arthroplasty. Among the 1242 patients randomized to receive one of seven postoperative regimens of milvexian (25 mg, 50 mg, 100 mg, or 200 mg twice daily or 25 mg, 50 mg, or 200 mg once daily) or enoxaparin (40 mg once daily), the primary efficacy outcome was a composite endpoint (including asymptomatic deep-vein thrombosis, confirmed symptomatic venous thromboembolism, or death from any cause), while the principal safety outcome was clinically relevant bleeding, a composite of major and clinically relevant non-major bleeding. In the milvexian twice daily arms, venous thromboembolism developed in 27 of 129 (21%) taking 25 mg, in 14 of 124 (11%) taking 50 mg, in 12 of 134 (9%) taking 100 mg, and in 10 of 131 (8%) taking 200 mg. In patients who received milvexian once daily, venous thromboembolism developed in 7 of 28 (25%) taking 25 mg, in 30 of 127 (24%) taking 50 mg, and in 8 of 123 (7%) taking 200 mg, as compared with 54 of 252 patients (21%) taking enoxaparin. No differences were found in terms of bleeding (4% in patients receiving milvexian and 4% in those taking enoxaparin). The rates of adverse events were similar in the milvexian (39%) and enoxaparin

**Table I** Pharmacokinetics and Pharmacodynamics Parameters of FXI Inhibitors

Drug Name	Antisense Oligonucleotides or ASO	Aptamers	Monoclonal Antibodies	Natural Inhibitors	Small Peptidomimetic Molecules
Target	FXI mRNA	FXIa	FXI or FXI synthesis	FXIa or FXIa + FXIIa	FXIa or FXI +plasma kallikrein
Mechanism	Specific protein synthesis blocking	Specific protein binding	Specific protein binding and decrease its concentration	Specific protein binding	Specific protein binding
Oral galenic formulation	No	No	No	No	Yes
Administration route	Administration route SC	Administration route IV or SC	Administration route IV or SC	Administration route IV	Administration route IV or oral
Half life	Long: Weekly administration	Short: Daily administration	Long: Monthly administration	Short: Daily administration	Short: Daily administration
Action	Slow and long acting	Fast and short acting	Fast and long-acting	Fast and short acting	Fast and short acting
Renal excretion	No	No	No	n/d	Biliary and 15% renal excretion
CYP metabolism	No	No	No	No	CYP <sub>3A4</sub>
Potential for drug-drug interactions	No	No	No	n/d	Midazolam Rifampicin Verapamil, Ketoconazole ...
Need and availability of antidote or of reversion strategy	Yes: FXI replacement	No	Yes: not existing failure of FXI replacement	No	No

(38%) groups, while the rates of serious adverse events were reported in 2% of the milvexian group and 4% of the enoxaparin group. The authors concluded that oral milvexian was effective for the prevention of venous thromboembolism, particularly with twice-daily regimen, and associated with a low risk of bleeding.

## Ongoing Studies

Based on the encouraging results of phase II trials performed in patients undergoing total-knee replacement surgery, FXI drugs are currently being evaluated in situations where the use of DOACs is discouraged,<sup>36,45–49</sup> particularly in patients with End-Stage Renal Disease and patients with Cancer-associated thrombosis.

The small molecule Milvexian is registered in 22 trials. Within these trials, especially patients with End-Stage Renal Disease (ESRD) under hemodialysis have been included (NCT03196206, NCT02902679).<sup>50</sup> These patients have an increased risk for VTE and are usually contraindicated for DOACs, because of drug bioaccumulation in patients with high bleeding risk.<sup>51</sup> Indeed, in five other registered studies ESDR patients are included for this reason: Asundexian (BAY2433334), Factor XI LICA (BAY 2976217), IONIS FXI-LRx (ISIS 416858), MK-2060 and Osocimab (BAY1213790).

Abelacimab is the first FXIa Inhibitor to be tested in Phase III studies (NCT05171049, NCT05171075), and both studies are conducted in patients with Cancer-associated thrombosis (CAT). CAT patients are both at an increased risk of recurrent VTE and anticoagulation-associated bleeding. Current guidelines advise cautious treatment of CAT patients with DOACs (apixaban, rivaroxaban or edoxaban), due to the increased bleeding risk, or to settle altogether for LMWH therapy.<sup>52</sup> The increased risk for anticoagulant-associated bleeding in CAT patients makes it apparent that there is a dire need for safer anticoagulants, and FXIa inhibitors could substantially improve patient care in this clinical scenario. In

Table 2 Published Phase I Trial for FXI Inhibitors

Registration Number	Patient Characteristics	Study	Drug Name	N	Endpoints	Conclusion
<i>Antibodies</i>						
NCT03097341	Healthy adult volunteers aged 18–48 yo	Lorentz et al 2019 <sup>39</sup>	Xisomab 3G3 (AB023)	21 N=16 active N= 5 placebo	<b>Safety</b> (Abnormal Vital Signs, Abnormal Electrocardiogram, Abnormal Injection Site Reaction, Abnormal Laboratory Values, Immunogenicity, death) <b>Tolerability</b> Pharmacokinetic parameters Pharmacodynamic parameters	There were no serious adverse events (SAEs) experienced in this study. No subjects were removed from the study due to adverse events (AEs). Overall, 10 of 21 (48%) subjects experienced a total of 20 TEAEs in this study, with 7 of 16 (44%) subjects following active treatment and 3 of 5 (60%) subjects following placebo
/	ANT-003 Healthy adult volunteers + obese patients (BMI ≥ 35 kg/m <sup>2</sup> ) aged 18-60 yo ANT-004 patients with atrial fibrillation or flutter CHA <sub>2</sub> DS <sub>2</sub> -VASc of 0–1 for men and 1–2 for women aged 18–85 yo	Yi et al 2022 <sup>40</sup> ANT-003 ANT-004	Abelacimab (MAA868)	32 ANT-003=24 ANT-004=8	As vital signs, adverse event assessments, laboratory tests, Pharmacokinetic parameters Pharmacodynamic parameters Anti-drug antibodies (ADA) assessment	The limitations of these studies include, by design, the single dose exposure in ANT-003 which limits the ability to detect clinically relevant safety signals. In addition, due to the COVID-19 pandemic, enrollment in the ANT-004 study was stopped early and thus the fully planned data set of PK, PD, and immunogenicity data for monthly subcutaneous administration of abelacimab could not be collected. Parenteral administration of abelacimab demonstrated a favorable safety profile with no clinically relevant bleeding events
<i>Antisense oligonucleotides or ASO</i>						
/	Healthy subjects aged 18–65 yo	Liu et al. 2011 <sup>57</sup>	ISIS-FXIRx	Single dose SC 50 mg/kg n=8 100 mg/kg n=8 200 mg/kg n=16 300 mg/kg n=8 8x SC injections n=12	Safety (adverse event (AE) clinical and laboratory tests safety, tolerability, pharmacokinetics and pharmacodynamics	No study drug related bleeding events were reported. No clinical or biological significant modification occurred. One serious AE (allergic reaction) occurred

<i>Small molecule</i>						
NCT03919890	Part A enrolled men only, Part B enrolled men or women of non-childbearing potential aged 18–55 yo	Beale et al 2021 <sup>58</sup>	ONO-7684	72 Part A n= 36 active n= 12 Part B n=24	Safety (adverse event (AE) reporting using the Medical Dictionary for Regulatory Activities (version 22.0), clinical laboratory tests (biochemistry, haematology and urinalysis), vital signs, electrocardiograms (ECGs), physical examination and cardiac telemetry) Tolerability Pharmacokinetic parameters Pharmacodynamic parameters	No signal on safety total of eight (16.7%) out of 48 fasted subjects and one (12.5%) out of eight fed subjects reported treatment-emergent adverse events (TEAEs) in Part A, and three (12.5%) of 24 subjects reported TEAEs in Part B (Table 2). There were no severe or serious TEAEs and no TEAEs that led to treatment discontinuation or interruption.
/	Healthy adult caucasian men Aged 18–45 yo	Thomas et al 2021 <sup>59</sup>	Asundexian (BAY2433334)	70 Part 1 n=56 active n=14 placebo; Part 2 n=16	Safety (symptomatic bleeding, signs of hepatobiliary dysfunction or pancreatic disorders, Tolerability Pharmacokinetic parameters Pharmacodynamic parameters	BAY 2433334 exhibited favorable safety and tolerability. BAY 2433334 dose-dependently inhibited FXIa activity and increased activated partial thromboplastin time.
/	Healthy adult caucasian men Aged 18–45 yo	Kubitza et al 2022 <sup>38</sup>	Asundexian (BAY2433334)	96 Parts A and B: n= 36 active; n=12 to placebo. Part C: n= 48 active plus midazolam	Safety (physical examination, vital signs, 12-lead electrocardiogram (ECG) and clinical laboratory evaluation) Tolerability Pharmacokinetic parameters Pharmacodynamic parameters Interaction with Midazolam	Multiple dosing of BAY 2433334 in healthy volunteers was well tolerated, with a predictable pharmacokinetic/ pharmacodynamic profile and no clinically relevant CYP3A4 induction or inhibition.

(Continued)

Table 2 (Continued).

Registration Number	Patient Characteristics	Study	Drug Name	N	Endpoints	Conclusion
/	Healthy adult volunteers: Aged 18–45 yo	Perera et al 2021 <sup>37</sup>	Milvexian (BMS- 986177) (JNJ70033093)	48 part A of the study (n = 24 active, n = 8 placebo). Part B (n = 32 active, n = 8 placebo)	Safety a medical review of adverse event (AE) reports and the results of clinical laboratory tests, vital sign measurements, ECGs, and physical examinations up to 48 h postdose. Events of special interest included clinically and nonclinically significant bleeding. AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0. Pharmacokinetic parameters Pharmacodynamic parameters	Administration were generally safe and well-tolerated. No deaths or other Severe AEs occurred during the study. All Treatment-emergent AEs were mild in severity.



**Table 3** Published Phase II Trial for FXI Inhibitors

DOAC short coming in VTE	Registration number	Study	Drug name	Comparator	N	End Point	Conclusion
Total Knee Replacement	<i>Anti-sens oligonucleotides</i>						
	NCT01713361 / EudraCT: 2012-001836-72	Büller et al <sup>42</sup> 2015 FXI-ASO TKA trial	IONIS FXI-LRx (ISIS 416858) 200 mg or 300 mg SC	Enoxaparin 40 mg	412	All DVT symptomatic PE, fatal PE, and unexplained death	Incidence of VTE - 27% in the 200-mg dose of FXI-ASO - 4% in the 300-mg dose of FXI-ASO, -30% of who received enoxaparin Bleeding - 3% in the 200-mg dose of FXI-ASO - 3% in the 300-mg dose of FXI-ASO, -8% of who received enoxaparin
	<i>Small molecule</i>						
	NCT03891524 / CR108600 / EudraCT: 2018-004237-32	Weitz et al <sup>44</sup> 2021 AXIOMATIC-TKR trial	Milvexian (BMS-986177) (JNJ70033093) oral 5 mg, 50 mg, 100 mg, or 200 mg twice daily or 25 mg, 50 mg, or 200 mg once daily	Enoxaparin 40 mg SC	1242	VTE, Bleeding Event, Major, CRNM and minimal bleeding Deaths	Incidence of VTE among those receiving Milvexian twice daily : -21% taking 25 mg -11% taking 50 mg -9% taking 100 mg -8% taking 200 mg. Incidence of VTE among those receiving Milvexian once daily: - 25% taking 25 mg - 24% taking 50 mg - 7% taking 200 mg - 21% taking enoxaparin. Any bleeding 4% taking milvexian 4% taking enoxaparin Any major bleeding or CRNMB -1% taking milvexian -2% taking enoxaparin Serious adverse events -2% taking milvexian -4% taking enoxaparin

(Continued)

Table 3 (Continued).

DOAC short coming in VTE	Registration number	Study	Drug name	Comparator	N	End Point	Conclusion
	<i>Antibody</i>						
	NCT03276143/ Sponsor: 17664 / EudraCT: 2016-002681-31	Weitz et al <sup>41</sup> 2020 FOXROT trial	Osocimab (BAY1213790) Single IV postoperative doses of 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg, or 1.8 mg/kg Single IV preoperative doses of 0.3 mg/kg or 1.8 mg/kg	40 mg of SC enoxaparin once daily or 2.5 mg of oral apixaban twice daily for at least 10 days or until venography	813	Composite endpoint of VTE events Composite endpoint of major and clinically relevant non-major bleeding	Incidence of VTE among patients taking Osocimab postoperative -23.7% receiving 0.3 mg/kg -15.7% receiving 0.6 mg/kg -16.5% receiving 1.2 mg/kg -17.9% receiving 1.8 mg/kg taking Osocimab preoperative -29.9% receiving 0.3 mg/kg -11.3% receiving 1.8 mg/kg Taking enoxaparin -26.3% receiving enoxaparin Taking apixaban -14.5% receiving Major or CRNMB -4.7% receiving Osocimab -5.9% receiving enoxaparin -2% receiving apixaban
	Sponsor : 129008 / EudraCT: 2019-003756-37	Verhamme et al <sup>45</sup> 2021 ANT-005 TKA trial	Abelacimab (MAA868) 30 mg, 75 mg, or 150 mg	Enoxaparin 40 mg SC	412	Composite endpoint of VTE events (asymptomatic DVT, symptomatic VTE, inexplicable death)	Incidence of VTE -13% in the 30-mg abelacimab group -5% in the 75-mg abelacimab group -4% in the 150-mg abelacimab group -22% in the enoxaparin group Bleeding 2% in the 30-mg 2% in the 75-mg of the patients in the abelacimab group No bleeding in the other group

<b>End Stage Renal Disease</b>	<i>Antibody</i>						
	NCT03612856	Lorentz et al 2021	Xisomab 3G3 (AB023) VTE prophylaxis during hemodialysis 0.25 mg/kg or 0.50 mg/kg	placebo	27	Bleeding of vascular access site	Bleeding 0% Receiving 0.25 mg.kg 62% Receiving 0.5 mg/kg 38% Receiving placebo
	<i>Small Molecule</i>						
	NCT03000673	/	Milvexian (BMS-986177) (JNJ70033093) VTE prophylaxis during hemodialysis 100 mg or 300 mg	UFH IV infusion enoxaparin 40 mg by SC	32	Adverse Events (AEs), Serious AEs (SAEs), AEs Leading to Discontinuation and Death	AE UFH IV infusion 6.25% enoxaparin 40 mg by SC 9.7% Milvexian 100mg 12.5% Milvexian 300 mg 13%
<i>Anti-sens oligonucleotides</i>							
NCT03358030 / EudraCT Number 2017-002165-21	/ ESMERALD trial	IONIS FXI-LRx (ISIS 416858) VTE prophylaxis during hemodialysis 200 mg, 250 mg or 300 mg	placebo	213	Safety, Tolerability Incidence of clinically relevant and non-major bleeding	No results posted	

addition, some oncologic patients suffer from variable oral route availability due to difficulties in swallowing or vomiting, which impairs correct administration of DOACs. Monoclonal antibodies such as Abrelacimab could provide a solution in these cases because of its monthly parenteral administration. CAT patients with cancer involving mucosa, such as gastrointestinal or genitourinary cancers, are at an even higher risk of bleeding than patients with other cancer types, which has been taken into account by Abrelacimab researchers by dedicating one phase III trials to this cohort (NCT05171075).<sup>53</sup> Another scenario in which FXI inhibition could be beneficial is that of cancer patients with Catheter-Related Thrombosis (CRT). The monoclonal antibody against FXIa, Xisomab 3G3 (AB023), has a Phase II trial ongoing to address the prevention of CRT in cancer patients (NCT04465760).

Table 4 summarises the most expected ongoing and non-published completed trials, particularly in patients with ESRD or CAT, situations in which FXI drugs seem to have a great potential. FXI inhibitors Milvexian (BMS-986177, JNJ70033093) and Abrelacimab (MAA868) can be regarded as the most advanced drugs, regarding their clinical development.

## Perspectives

Phase III trials on so-called frail patients, such as elderly, critical care, or septic patients have not yet been put in motion. These patients suffer from an increased anticoagulant-related bleeding, so they could benefit from safer profile anticoagulants as FXIa inhibitors.<sup>54</sup> Despite their common referral as frail patients, these groups also differ in drug pharmacokinetic profile needs. Elderly patients would benefit from a drug with a non-aggressive metabolic impact on the blockage of the coagulation balance in order to avoid adverse effects (AEs) derived from pharmacodynamic (PD) and pharmacokinetic (PK) changes that characterize aged population. These PD and PK changes include an increased sensitivity to anticoagulants on the one hand, and a diminished renal and hepatic clearance on the other, thus why perhaps a drug with a “Slow onset – Fast offset” pharmacokinetic (PK) profile could improve the safety profile of DOACs. Perhaps in the development of new FXIa inhibitors, a good candidate will arise that allows for a progressive introduction and easy reversal in case of bleeding to avoid adverse effects. In contrast, critical care and septic patients require a “Fast onset - Fast offset” PK profile. Aptamers and small molecules that inhibit FXIa display this specific profile while administration of the drug is parenteral, overcoming oral route unavailability that is frequently present in these patients. However, it is unclear whether FXIa inhibitors would be beneficial over the current standard of care, Heparins, that already have a fitting PK and safety profile, and parenteral administration. Dedicated monitoring would be needed.

For pregnant and breastfeeding VTE patients, another group in which DOACs are contraindicated, the use of FXI inhibitors should be explored. Known problematic scenarios regarding the inefficacy of DOACs, such as mechanical heart valve, cardiac assist devices, ECMO therapy and noncancer CRT patients, are englobed under the term “Artificial Contact Surfaces Associated Thrombosis” (ACSAT). These patients may benefit profoundly from an anticoagulant strategy based on inhibition of FXI, since these drugs target the factor that is activated as a direct result of contact activation. For ACSAT, researchers have even advocated the use of FXIIa inhibitors over FXIa because of their negligible associated risk for bleeding. However, additional research is needed to test the efficacy of FXII inhibitors to prevent VTE in these specific clinical scenarios.<sup>48,49</sup>

FXI antagonizing drugs may also become an interesting option as “One Shot” therapies in situations where a short period of treatment is desired, as an alternative to a prophylactic or intermediate dose of daily Fondaparinux or LWMH injections (e.g superficial venous thrombosis, post-operative thromboprophylaxis).<sup>47,55</sup> Some FXIa inhibitors like monoclonal antibodies could be active for 30–45 days after being administered once subcutaneously.

## Conclusion

Based on available data, FXI drugs show great promise. However, confirmation of their efficacy in dedicated randomized controlled trials is needed. Importantly, if the expected advantage of FXIa inhibitors is to be safer than DOACs, they are not exempt from bleeding risk, and dedicated reversal strategies are needed.<sup>56</sup> Especially for “slow offset” molecules like antibodies or ASOs, development of a reliable reversal strategy based on antidote drugs is required. To our knowledge, only a single suspended trial on Milvexian antidote research has been registered so far (NCT04543383). Most of the cited studies are either completed with no published results or scheduled to be completed as late as 2024. It is therefore not unreasonable that we will incorporate FXIa inhibitors into daily clinical practice in the following 3–4 years, and that we can expect changes in VTE clinical guidelines accordingly.

**Table 4** Ongoing Studies Assessing Anti-FXI Drugs in the Prevention of Thrombosis

Setting	Trial ID	Phase	Molecule Name	Study Name	Molecule Type	Regimen	Comparator	N	Primary Endpoints	Status
Cancer-associated thrombosis	NCT05171075	III	Abelacimab (MAA868)	MAGNOLIA trial	Ab	I.V/S.C	Dalteparin	1020	Time to VTE	Upcoming
	NCT05171049	III	Abelacimab (MAA868)	ASTER trial	Ab	I.V/S.C	Apixaban	1655	Time to VTE	Upcoming
	NCT04465760	II	Xisomab 3G3 (AB023)	/	Ab	I.V	None	50	Incidence of CRT	Ongoing
End-stage renal disease	NCT04534114	II	Factor XI LICA (BAY 2976217)	/	ASO	S.C	Placebo	305	Major and CRNM bleeding events	Upcoming
	NCT02553889	II	IONIS FXI-LRx (ISIS 416858)	/	ASO	S.C	Placebo	49	Frequency and severity of Adverse events (including bleeding events)	Completed
	NCT03196206	I	Milvexian (BMS-986177)	/	Small molecule	ORALLY	Enoxaparin	33	PK parameters	Completed
	NCT02902679	I	Milvexian (BMS-986177)	/	Small molecule	ORALLY	None	6	Number of subjects with Adverse events (AEs)	Completed
	NCT03873038	I	MK-2060	MK-2060-004	Ab	I.V	Placebo	38	Percentage of Participants with Any Adverse Event	Completed
	NCT05027074	II	MK-2060	MK-2060-007	Ab	I.V	Placebo	489	Time to thrombosis of the arteriothrombosis graft	Ongoing
	NCT03787368	I	Osocimab (BAY1213790)	/	Ab	I.V	Placebo	55	Major and CRNM bleeding events	Completed
	NCT04523220	II	Osocimab (BAY1213790)	/	Ab	S.C	Placebo	686	Major and CRNM bleeding events	Upcoming
	NCT04510987	I	BAY2433334 (Asundexian)	/	Small molecule	ORALLY	None	48	PK parameters	Completed

**Abbreviations:** Ab, antibodies; I.V, intravenous; S.C, subcutaneous; CRNM, clinically relevant non major; PK, pharmacokinetic.

## Disclosure

The authors report no conflicts of interest in this work.

## References

- Weitz JI, Jaffer IH, Fredenburgh JC. Recent advances in the treatment of venous thromboembolism in the era of the direct oral anticoagulants. *F1000Research*. 2017;6. doi:10.12688/F1000RESEARCH.11174.1/DOI
- Hindricks G, Potpara T, Dagres N, et al. ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020;2020:373–498. doi:10.1093/eurheartj/ehaa612
- Konstantinides SV, Meyer G, Becattini C, et al. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41(4):543–603. doi:10.1093/eurheartj/ehz405
- Stevens SM, Woller SC, Baumann Kreuziger L, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report – executive summary. *Chest*. 2021;160:e545–e608. doi:10.1016/j.chest.2021.07.056
- Bertoletti L, Gusto G, Khachatryan A, et al. Effectiveness and safety of oral anticoagulants in the treatment of acute venous thromboembolism: a nationwide comparative cohort study in France. *Thromb Haemost*. 2022. doi:10.1055/a-1731-3922
- Koziel M, Teutsch C, Bayer V, et al. Changes in anticoagulant prescription patterns over time for patients with atrial fibrillation around the world. *J Arrhythmia*. 2021;37(4):990–1006. doi:10.1002/joa3.12588
- Bertoletti L, Ollier E, Duvallard C, et al. Direct oral anticoagulants: current indications and unmet needs in the treatment of venous thromboembolism. *Pharmacol Res*. 2017;118:33–42. doi:10.1016/j.phrs.2016.06.023
- Al-Samkari H, Connors J. The role of direct oral anticoagulants in treatment of cancer-associated thrombosis. *Cancers*. 2018;10(8):271. doi:10.3390/cancers10080271
- Levi M. Management of bleeding in patients treated with direct oral anticoagulants. *Crit Care*. 2016;20(1):249. doi:10.1186/s13054-016-1413-3
- Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban pharmacokinetics at steady state in hemodialysis patients. *J Am Soc Nephrol*. 2017;28(7):2241–2248. doi:10.1681/ASN.2016090980
- Speed V, Roberts LN, Patel JP, Arya R. Venous thromboembolism and women's health. *Br J Haematol*. 2018;183(3):346–363. doi:10.1111/bjh.15608
- Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214. doi:10.1056/NEJMoa1300615
- Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood*. 2018;132(13):1365–1371. doi:10.1182/blood-2018-04-848333
- Gailani D, Renné T. The intrinsic pathway of coagulation: a target for treating thromboembolic disease? *J Thromb Haemost*. 2007;5(6):1106–1112. doi:10.1111/j.1538-7836.2007.02446.x
- Davie EW, Ratnoff OD. Waterfall sequence for intrinsic blood clotting. *Science*. 1964;145(3638):1310–1312. doi:10.1126/science.145.3638.1310
- Wolberg AS, Rosendaal FR, Weitz JI, et al. Venous thrombosis. *Nat Rev Dis Prim*. 2015;1:15006. doi:10.1038/nrdp.2015.6
- Tillman BF, Gruber A, McCarty OJT, Gailani D. Plasma contact factors as therapeutic targets. *Blood Rev*. 2018;32(6):433–448. doi:10.1016/j.blre.2018.04.001
- Maas C, Oschatz C, Renné T. The plasma contact system 2.0. *Semin Thromb Hemost*. 2011;37(04):375–381. doi:10.1055/s-0031-1276586
- Fritsma GA, Dembitzer FR, Randhawa A, et al. Recommendations for appropriate activated partial thromboplastin time reagent selection and utilization. *Am J Clin Pathol*. 2012;137(6):904–908. doi:10.1309/AJCP3J1ZKYBFQXJM
- Lewandowska MD, Connors JM. Factor XI Deficiency. *Hematol Oncol Clin North Am*. 2021;35(6):1157–1169. doi:10.1016/j.hoc.2021.07.012
- Renné T, Pozgajovic M, Gruner S, et al. Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med*. 2005;202(2):271–281. doi:10.1084/jem.20050664
- Zhang H, Löwenberg EC, Crosby JR, et al. Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. *Blood*. 2010;116(22):4684–4692. doi:10.1182/blood-2010-04-277798
- Cheng Q, Tucker EI, Pine MS, et al. A role for factor XIIa-mediated factor XI activation in thrombus formation in vivo. *Blood*. 2010;116(19):3981–3989. doi:10.1182/blood-2010-02-270918
- David T, Kim YC, Ely LK, et al. Factor XIa-specific IgG and a reversal agent to probe factor XI function in thrombosis and hemostasis. *Sci Transl Med*. 2016;8:353. doi:10.1126/scitranslmed.aaf4331
- Fuchs TA, Brill A, Duerschmied D, et al. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci*. 2010;107(36):15880–15885. doi:10.1073/pnas.1005743107
- Kannemeier C, Shibamiya A, Nakazawa F, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci*. 2007;104(15):6388–6393. doi:10.1073/pnas.0608647104
- Müller F, Mutch NJ, Schenk WA, et al. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. *Cell*. 2009;139(6):1143–1156. doi:10.1016/j.cell.2009.11.001
- Maas C, Govers-Riemslog JWP, Bouma B, et al. Misfolded proteins activate factor XII in humans, leading to kallikrein formation without initiating coagulation. *J Clin Invest*. 2008. doi:10.1172/JCI35424
- Müller F, Gailani D, Renné T. Factor XI and XII as antithrombotic targets. *Curr Opin Hematol*. 2011;18(5):349–355. doi:10.1097/MOH.0b013e3283497e61
- Gailani D, Broze GJ. Factor XI activation in a revised model of blood coagulation. *Science*. 1991;253(5022):909–912. doi:10.1126/science.1652157
- von Brühl M-L, Stark K, Steinhart A, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med*. 2012;209(4):819–835. doi:10.1084/jem.20112322
- Geddings JE, Hisada Y, Boulaftali Y, et al. Tissue factor-positive tumor microvesicles activate platelets and enhance thrombosis in mice. *J Thromb Haemost*. 2016;14(1):153–166. doi:10.1111/jth.13181
- Martinod K, Wagner DD. Thrombosis: tangled up in NETs. *Blood*. 2014;123(18):2768–2776. doi:10.1182/blood-2013-10-463646

34. Sridhar DC, Abou-Ismaïl MY, Ahuja SP. Central venous catheter-related thrombosis in children and adults. *Thromb Res.* 2020;187:103–12. doi:10.1016/j.thromres.2020.01.017
35. Olson SR, Murphree CR, Zonies D, et al. Thrombosis and bleeding in extracorporeal membrane oxygenation (ECMO) without anticoagulation: a systematic review. *ASAIO J.* 2021;67(3):290–296. doi:10.1097/MAT.0000000000001230
36. Fredenburgh JC, Weitz JI. New anticoagulants: moving beyond the direct oral anticoagulants. *J Thromb Haemost.* 2021;19(1):20–29. doi:10.1111/jth.15126
37. Perera V, Wang Z, Luetzgen J, et al. First-in-human study of milvexian, an oral, direct, small molecule factor XIa inhibitor. *Clin Transl Sci.* 2021;15:330–342. doi:10.1111/cts.13148
38. Kubitz D, Heckmann M, Distler J, Koechel A, Schwerts S, Kanefendt F. Pharmacokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: a randomized Phase I multiple-dose study. *Br J Clin Pharmacol.* 2022. doi:10.1111/bcp.15230
39. Lorentz CU, Verbout NG, Wallisch M, et al. Contact activation inhibitor and factor xi antibody, AB023, produces safe, dose-dependent anticoagulation in a phase I first-in-human trial. *Arterioscler Thromb Vasc Biol.* 2019;39(4):799–809. doi:10.1161/ATVBAHA.118.312328
40. Yi BA, Freedholm D, Widener N, et al. Pharmacokinetics and pharmacodynamics of Abelaicimab (MAA868), a novel dual inhibitor of factor XI and factor XIa. *J Thromb Haemost.* 2022;20(2):307–315. doi:10.1111/jth.15577
41. Weitz JI, Bauersachs R, Becker B, et al. Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty. *JAMA.* 2020;323(2):130. doi:10.1001/jama.2019.20687
42. Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med.* 2015;372(3):232–240. doi:10.1056/NEJMoa1405760
43. Verhamme P, Yi BA, Segers A, et al. Abelaicimab for prevention of venous thromboembolism. *N Engl J Med.* 2021;385(7):609–617. doi:10.1056/NEJMoa2105872
44. Weitz JI, Strony J, Ageno W, et al. Milvexian for the prevention of venous thromboembolism. *N Engl J Med.* 2021;385(23):2161–2172. doi:10.1056/NEJMoa2113194
45. Al-Horani RA. Factor XI(a) inhibitors for thrombosis: an updated patent review (2016-present). *Expert Opin Ther Pat.* 2020;30(1):39–55. doi:10.1080/13543776.2020.1705783
46. Al-Horani RA. Targeting factor XI(a) for anticoagulation therapy: a patent landscape. *Pharm Pat Anal.* 2020;9(1):3–5. doi:10.4155/ppa-2020-0002
47. Mackman N, Bergmeier W, Stouffer GA, Weitz JI. Therapeutic strategies for thrombosis: new targets and approaches. *Nat Rev Drug Discov.* 2020;19(5):333–352. doi:10.1038/s41573-020-0061-0
48. Srivastava P, Gailani D. The rebirth of the contact pathway: a new therapeutic target. *Curr Opin Hematol.* 2020;27(5):311–319. doi:10.1097/MOH.0000000000000603
49. Weitz JI, Chan NC. Novel antithrombotic strategies for treatment of venous thromboembolism. *Blood.* 2020;135(5):351–359. doi:10.1182/blood.2019000919
50. Ribic C, Crowther M. Thrombosis and anticoagulation in the setting of renal or liver disease. *Hematology.* 2016;2016(1):188–195. doi:10.1182/asheducation-2016.1.188
51. Catella J, Bertoletti L, Mismetti P, et al. Severe renal impairment and risk of bleeding during anticoagulation for venous thromboembolism. *J Thromb Haemost.* 2020;18:1728–1737. doi:10.1111/jth.14837
52. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. *J Clin Oncol.* 2020;38(5):496–520. doi:10.1200/JCO.19.01461
53. Kraaijpoel N, van Es N, Bleker S, et al. Clinical impact and course of anticoagulant-related major bleeding in cancer patients. *Thromb Haemost.* 2018;118(01):174–181. doi:10.1160/TH17-04-0274
54. Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the improve investigators. *Chest.* 2011;139(1):69–79. doi:10.1378/chest.09-3081
55. Decousus H, Prandoni P, Mismetti P, et al. Fondaparinux for the treatment of superficial-vein thrombosis in the legs. *N Engl J Med.* 2010;363(13):1222–1232. doi:10.1056/NEJMoa0912072
56. Salomon O, Gailani D. A proposal for managing bleeding in patients on therapeutic factor XI(a) inhibitors. *J Thromb Haemost.* 2022;20(1):32–38. doi:10.1111/jth.15579
57. Liu Q, Bethune C, Dessouki E, Grundy J, Monia BP, Bhanot S. ISIS-FXIRx, A novel and specific antisense inhibitor of factor XI, caused significant reduction in FXI antigen and activity and increased aPTT without causing bleeding in healthy volunteers. *Blood.* 2011;118(21):209. doi:10.1182/BLOOD.V118.21.209.209
58. Beale D, Dennison J, Boyce M, et al. ONO-7684 a novel oral FXIa inhibitor: safety, tolerability, pharmacokinetics and pharmacodynamics in a first-in-human study. *Br J Clin Pharmacol.* 2021;87(8):3177–3189. doi:10.1111/bcp.14732
59. Thomas D, Kanefendt F, Schwerts S, Unger S, Yassen A, Boxnick S. First evaluation of the safety, pharmacokinetics, and pharmacodynamics of BAY 2433334, a small molecule targeting coagulation factor XIa. *J Thromb Haemost.* 2021;19(10):2407–2416. doi:10.1111/jth.15439
60. Lorentz CU, Tucker EI, Verbout NG, et al. The contact activation inhibitor AB023 in heparin-free hemodialysis: results of a randomized Phase 2 clinical trial. *Blood.* 2021;138(22):2173–2184. doi:10.1182/BLOOD.2021011725

## Vascular Health and Risk Management

Dovepress

### Publish your work in this journal

Vascular Health and Risk Management is an international, peer-reviewed journal of therapeutics and risk management, focusing on concise rapid reporting of clinical studies on the processes involved in the maintenance of vascular health; the monitoring, prevention and treatment of vascular disease and its sequelae; and the involvement of metabolic disorders, particularly diabetes. This journal is indexed on PubMed Central and MedLine. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/vascular-health-and-risk-management-journal>