Factor XI inhibitors: cardiovascular perspectives

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Graphical Abstract

Possible forthcoming therapeutic indications for FXI/XIa inhibitors.
Abstract

Anticoagulants are the cornerstone for prevention and treatment of thrombosis but are not completely effective, and concerns about the risk of bleeding continue to limit their uptake. Animal studies and experience from patients with genetic coagulation factor XI deficiency suggesting that this factor is more important for thrombosis than for haemostasis raises the potential for drugs that target factor XI to provide safer anticoagulation. Multiple factor XI inhibitors are currently under evaluation in clinical trials, including parenterally administered antisense oligonucleotides, monoclonal antibodies, and orally active small-molecule inhibitors. Promising results of phase 2 trials in patients undergoing major orthopaedic surgery, and in those with end-stage kidney disease, atrial fibrillation and acute coronary syndromes have led to large phase 3 trials that are currently ongoing. We here review premises for the use of these agents, results so far accrued, ongoing studies, and perspectives for future patient care.

Keywords

Anticoagulation • Anticoagulants • Antithrombotic agents • Thrombosis • Bleeding • Factor XI

Introduction

Heparins and vitamin K antagonists (VKAs) were the only widely available anticoagulants for more than 70 years. In the past three decades, new parenteral and oral anticoagulants have been introduced, including designer drugs that target individual coagulation proteins. The first major group of designer anticoagulants to be introduced into clinical practice were the direct oral anticoagulants (DOACs) which target either thrombin or activated coagulation factor X (FXa). To address remaining unmet needs, recent attention has focused on coagulation factor XI (FXI) as a novel target for new anticoagulants.

This review examines unmet needs related to the use of DOACs, the promise of FXI as a new therapeutic target, the pharmacological features of drugs in development that target FXI, and their possible therapeutic indications. Information included in this review is based on literature published up to 15 June 2022.

Current status of DOACs and unmet needs

DOACs—which include apixaban, dabigatran, edoxaban and rivaroxaban—were shown in randomized trials involving over one-hundred thousand patients to be at least as effective as heparins and warfarin for the prevention of stroke in patients with atrial fibrillation and the prevention and treatment of venous thromboembolism (VTE), and were associated with lower rates of intracranial bleeding, which translated into reduced mortality. In addition, low-dose rivaroxaban given in combination with antiplatelet therapy was shown to be effective for the prevention of major adverse cardiovascular events and mortality in patients with a recent acute coronary syndrome and in those with chronic coronary or peripheral artery disease. DOACs also have important practical advantages; they are more convenient than heparins and warfarin because they can be given orally in fixed doses without the need for routine coagulation monitoring, and they have a low propensity for food and drug interactions. Accordingly, these drugs are now preferred for most indications.

Despite their remarkable success, DOACs still have limitations, including areas where unfavourable results were reported (e.g. in patients with mechanical heart valves, the antiphospholipid syndrome); patients at high risk for bleeding (overall DOACs increased risk of gastrointestinal bleeding compared with VKAs); settings in which DOACs have not been adequately tested (e.g. extremes of renal function, impaired liver function, extremes of body weight); still non-negligible interactions with other drugs, and indications not yet fully tested in clinical trials (e.g. mitral stenosis, with or without atrial fibrillation).

In essence, despite considerable convenience and safety advantages DOACs are incompletely effective for thrombosis prevention, and treatment still causes bleeding, mainly gastrointestinal, limiting their use.

The contact pathway as a target for new agents

The potential to develop new agents with even better safety than DOACs, and possibly achieving the holy grail of preventing thrombosis without increasing the risk of bleeding, derives from knowledge of rare genetic disorders, specifically deficiency of the contact pathway coagulation protein FXI, which appears to be associated with reduced risk of thrombosis and only minor bleeding tendency.

FXI deficiency, also called haemophilia C (or Rosenthal disorder), to distinguish it from FXIII deficiency (haemophilia A) and FXII deficiency (haemophilia B), was first described in the 1950s in four generations of patients experiencing bleeding during surgery or dental extractions. Its prevalence is of one case every 100,000 people, although a higher frequency has been reported in some populations, including Ashkenazi and Iraqi Jews, reaching 8–9%. In classical coagulation tests, correction of the coagulation defect occurred when plasma of these patients was mixed with plasma of patients with haemophilia A or B, thereby suggesting deficiency of another coagulation protein. This was originally named ‘plasma thromboplastin antecedent’, and then FXI. Unlike haemophilia A or B, which are chromosome X-linked, this disorder has an autosomal inheritance pattern and is associated with a mild and variable bleeding tendency despite FXI levels of <20%.

Despite minimal bleeding propensity, routine laboratory tests are markedly abnormal in patients with FXI deficiency. FXI is part of the contact pathway of coagulation. FXI deficiency prolongs the activated partial thromboplastin time (aPTT) but does not affect the prothrombin time assay, which is primarily a measure of the tissue factor pathway of coagulation activation.

Inherited FXI deficiency can exacerbate trauma-induced bleeding in some individuals, complicating injuries, surgical procedures and childbirth, and can also contribute to menorrhagia. The pattern of bleeding in affected patients suggests that FXI serves a minor ancillary role in haemostasis in most circumstances. However, it is not possible to reliably distinguish congenital FXI-deficient patients who may bleed from those without an increased risk of bleeding.

On the other hand, evidence has been provided for FXI activation in conditions of atherothrombosis, such as myocardial infarction (also reviewed in), thus providing a rationale for interfering with a step in coagulation activated in the course of an atherothrombotic event.

Factor XI inhibitors
Thrombosis, as epitomized in the Virchow’s triad, is most commonly triggered following injury or disruption of the vessel wall (as in ruptured atherosclerotic plaques) exposing tissue factor (TF), also expressed on leukocytes, microvesicles, or diseased endothelial cells (vessel wall changes); as well as by stasis, as occurs in the left atrial appendage in atrial fibrillation and in peripheral veins in cases of venous thrombosis (changes in blood rheology); and in hypercoagulable states (the vulnerable blood). Unlike haemostasis, the growth and propagation of pathological thrombosis appears to be substantially dependent on the ability of FXI to amplify thrombin generation. The activation of TF-induced coagulation following plaque rupture results in a local thrombin burst, which acts in a positive feedback to activate FXI. In a growing thrombus, naturally occurring polyanions, such as DNA extruded from activated neutrophils (neutrophil extracellular traps, NETs) or inorganic phosphates (polyphosphates) released from activated platelets further amplify thrombin formation via the contact pathway, thereby rendering FXI an attractive target to attenuate thrombus growth. This also provides a rationale for targeting FXI as a way to uncouple thrombosis from hemostasis\(^22\) (Figure 1). Targeting the contact phase also appears to be logical in cases when thrombosis is triggered by exposure of blood to artificial surfaces (e.g. haemodialysis circuits, catheters, cardiopulmonary bypass, mechanical valves).

### Why FXI targeting may prevent thrombosis without increasing bleeding

Thrombosis, as epitomized in the Virchow’s triad, is most commonly triggered following injury or disruption of the vessel wall (as in ruptured atherosclerotic plaques) exposing tissue factor (TF), also expressed on leukocytes, microvesicles, or diseased endothelial cells (vessel wall changes); as well as by stasis, as occurs in the left atrial appendage in atrial fibrillation and in peripheral veins in cases of venous thrombosis (changes in blood rheology); and in hypercoagulable states (the vulnerable blood). Unlike haemostasis, the growth and propagation of pathological thrombosis appears to be substantially dependent on the ability of FXI to amplify thrombin generation. The activation of TF-induced coagulation following plaque rupture results in a local thrombin burst, which acts in a positive feedback to activate FXI. In a growing thrombus, naturally occurring polyanions, such as DNA extruded from activated neutrophils (neutrophil extracellular traps, NETs) or inorganic phosphates (polyphosphates) released from activated platelets further amplify thrombin formation via the contact pathway, thereby rendering FXI an attractive target to attenuate thrombus growth. This also provides a rationale for targeting FXI as a way to uncouple thrombosis from hemostasis\(^22\) (Figure 1). Targeting the contact phase also appears to be logical in cases when thrombosis is triggered by exposure of blood to artificial surfaces (e.g. haemodialysis circuits, catheters, cardiopulmonary bypass, mechanical valves).

### Pharmacology of FXI inhibitors in clinical development

FXI inhibitors can be classified into three major categories, based on their chemical structure (Table 1 and Figure 2): (i) ASOs, (ii) mAbs, (iii) small molecules. In addition, natural inhibitors and aptamers targeting FXI are undergoing pre-clinical development (Table 1). Small molecules that target FXa do not lower FXI levels, whereas ASOs reduce FXI synthesis and thereby lower FXI levels. These and other differences

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**Figure 1** The disconnect between haemostasis and thrombosis in the presence of factor XI (FXI) inhibition. (A) A large thrombin burst following traumatic vessel wall injury is sufficient to induce haemostatic plug formation without requiring amplification of thrombin generation via the contact pathway. (B) Conversely, a modest thrombin burst following disruption of atherosclerotic plaque requires amplification via the contact pathway to induce pathological thrombus formation. Inhibitors of the synthesis or activity of FXI (FXI/FXIa i), by partially reducing FXI levels or activity, may thus achieve thrombosis inhibition without impairing haemostasis.
in the pharmacological properties of drugs that target FXI have potential implications with respect to their therapeutic indications, as well as to their safety profile. Beside the risk of bleeding, adverse events related to the specific pharmacological classes need to be considered: specifically, mAbs can be immunogenic and might drive acute injection site and (auto)immune reactions; ASOs can exert proinflammatory effects and induce nephrotoxicity, hepatotoxicity and thrombocytopenia. Despite this, ASOs, mAbs, small molecules, and natural compounds have been safely evaluated in early-stage clinical trials, whereas aptamers that target FXI are yet to be tested in humans.

The Factor ELeven Inhibitory APtamer (FELIAP) is a DNA aptamer designed to inhibit FXIa-catalysed S2366 cleavage by binding at or near its active site with high affinity. Although its potency is limited, FELIAP has been considered as a lead compound for the development of more potent FXIa-inhibiting similar compounds. Two RNA aptamers (11.16 and 12.7) were developed as non-competitive inhibitors of FXIa, binding the FXIa anion-binding site (ABS2) of the catalytic domain and a charged area on the FXIa autolysis loop. Despite the interest in aptamer development, existing agents in such class have important pharmacokinetic limitations and are renally cleared, making them less attractive for clinical evaluation. They will not, therefore, be further discussed here below.

### Antisense oligonucleotides

ASOs are RNA molecules that bind to a cellular mRNA, thus preventing translation and reducing levels of the expressed protein. Two anti-FXI ASOs, IONIS-FXI RX and fesomersen, have been tested in clinical trials.

#### Figure 2

**Mechanism of action of FXI(a) inhibitors currently in development.** A, apple domain; CD, catalytic domain.
IONIS-FXI	extsubscript{RX}

IONIS-FXI	extsubscript{RX} (also known as FXI-ASO; BAY2306001, ISIS-416858) is the first FXI-inhibiting ASO reaching phase 2 evaluation. It is a 2′-O-(2-methoxyethyl) (2′-O-MOE) ASO that targets FXI mRNA in the liver, thus reducing FXI plasma concentrations in a dose-dependent manner. The maximum reduction occurs 3–4 weeks after the start of treatment, and the effects are prolonged for several weeks after treatment discontinuation.

Fesomersen

Fesomersen (IONIS-FXI-LaRX, FXI-LICA) is a second-generation ASO with a triantennary structure (having the form of three antennae) and N-acetyl galactosamine conjugation. By binding to the asialoglycoprotein receptor in the liver, this ligand-conjugated ASO is more potent than the unconjugated molecule, thereby allowing less frequent administrations (once a month or less, subcutaneously).

Monoclonal antibodies

mAbs with high specificity and affinity for coagulation FXI have shown promise in the prevention and treatment of thrombosis.

Osocimab (aka BAY 1213790) is a human immunoglobulin G1 mAb generated using phage display, that binds to a region adjacent to the active site of FXIa, thereby causing substantial structural changes. Osocimab has a rapid onset of action (mean time-to-peak plasma concentrations of 1–4 h), with a half-life of 30–44 days.

Abelacimab (aka MAA868) is a human mAb that binds to the catalytic domain of FXI and locks it in the zymogen (inactive precursor) conformation. When administered intravenously, abelacimab has a half-life of 25–30 days, allowing monthly administrations (or single administration, in the post-operative setting).

Xisomab 3G3 (aka AB023) is another mAb that reached phase 2 evaluation in end-stage renal disease (ESRD) patients. It is a recombinant humanized mAb that binds to the apple 2 (A2) domain of FXI and FXIa, thus blocking factor Xlla-mediated FXI activation in a concentration-dependent manner, inhibiting neither FXI activation by thrombin nor the procoagulant function of FXIa. In a phase 1 trial (NCT03097341), a dose-dependent aPTT prolongation was observed, but prothrombin time and bleeding time were not increased, suggesting no off-target effects on the TF pathway. Anticoagulation was maintained for over 1 month after the highest dose, thus confirming a durable effect.

A fourth mAb (MK-2060) is under clinical investigation in phase 1 and phase 2 trials of elderly patients with ESRD requiring haemodialysis (MK-2060-004 trial, NCT03873038; MK-2060-007 trial, NCT05027074). Moreover, a phase 1 trial is ongoing to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of the anti-FXI mAb REGN9933 in healthy volunteers (NCT05102136).

Small molecules

Unlike mAbs, small molecules have a limited molecular weight (upper limit of ~900 Da), allowing them to rapidly diffuse across membranes and to reach intracellular sites of action, with a consequent rapid onset and offset of action. Unlike ASOs and mAbs, which require injection, small molecules can be administered orally. Considering that FXIa is a polypeptide with a trypsin-like catalytic domain sharing structural similarities with prekallikrein, small molecules against FXIa have been designed to ensure high selectivity against FXIa, while not targeting prekallikrein.

Milvexian (aka BMS-986177/JNJ-70033093) is an active site, highly selective reversible inhibitor of human FXIa administered orally. In a phase 1 trial on healthy individuals (NCT02608970), milvexian reached the peak of plasma concentration 3–4 h after administration, according to the feeding state, with a terminal half-life of 8.3–13.8 h.

Asundexian (aka BAY 2433334) is another orally administered chemically synthesized small molecule, which directly, potently, and reversibly inhibits FXIa. The complete bioavailability of asundexian is unaffected by tablet formulation, gastric pH or food.

Other small molecules

Two other orally bioavailable small molecules, ONO-7684 and SHR2285, are currently under investigation. ONO-7684 is a competitive and reversible FXIa inhibitor (Ki = 0.002 μmol/L) with an attractive pharmacodynamic and safety profile, as shown in a first phase 1 trial in humans (NCT03919890). SHR2285, after being tested in three phase-1 trials in healthy volunteers (NCT04229433, NCT03769831, NCT04472819), has been tested also in other two phase-1 studies recently completed (NCT04829305, NCT04945616). The drug has also been tested in combination with aspirin and clopidogrel or ticagrelor. In a recently published single-center, randomized, double-blind, placebo-controlled trial conducted in China on 52 healthy subjects, the association of SHR2285 with aspirin, clopidogrel or ticagrelor was well tolerated. There was no significant effect on prothrombin time (PT) or international normalized ratio (INR), with no increased risk of bleeding.

EP-7041 is an intravenously administered, potent, highly selective inhibitor of FXIa (IC50 of 7.1 nM), with a rapid onset and offset of action (~45 min following a single IV bolus). EP-7041 is under investigation in an open-label phase 2 trial as thromboprophylaxis in patients with coronavirus disease 2019 (COVID-19) who require intensive care unit management (NCT05040776).

BMS-962212 is a direct, reversible, selective FXIa inhibitor, characterized by a rapid onset of action (mean time to peak concentration being of 1–2 h) and a short half-life (2–5 h following a single infusion) (NCT03197779), which make it a promising candidate for investigational use as an acute antithrombotic agent.

Natural inhibitors

Natural FXIa inhibitors include molecules derived from nematodes (acoshNAP10), snakes (fasciotor), bats (desmolans), and ticks (boophilin, and lXodes ricinus contact phase inhibitor, Ir-CPI). Similar to ASOs and mAbs, natural inhibitors require parenteral administration via subcutaneous or intravenous injection; however, differently from the first two classes, natural inhibitors feature a rapid onset and offset of action, and should therefore be administered on a daily base. Among them, only Ir-CPI has reached clinical phases of investigation. Ir-CPI is a serine protease inhibitor expressed by the salivary glands of the tick lXodes Ricinus, and acts as an inhibitor of the coagulation contact phase. Indeed, Ir-CPI has a Kunitz domain that is similar to the domains present in tissue factor pathway inhibitor (TFPI), and is a dual inhibitor of FXIIa and FXIa. Following favourable results of in vitro and in vivo studies, a phase 1 trial is currently ongoing to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of Ir-CPI in healthy males (NCT04653766).

Clinical trials of drugs that target factor XI

Potential future indications for drugs that target coagulation FXI are summarized in the Graphical Abstract, and ongoing studies, summarized in Tables 2–4, are briefly described in the following context.
Table 2

<table>
<thead>
<tr>
<th>Compound/ company</th>
<th>Indication</th>
<th>Clinical trial</th>
<th>Safety data</th>
<th>Efficacy data</th>
</tr>
</thead>
<tbody>
<tr>
<td>IONIS-FXI</td>
<td>Post-operative</td>
<td>NCT01713361</td>
<td>Safety data</td>
<td>Efficacy data</td>
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Prevention of venous thromboembolism in major orthopaedic surgery

The clinical development of new anticoagulants traditionally begins in patients undergoing joint replacement surgery, such as total knee arthroplasty (TKA). This procedure is associated with a high risk of post-operative VTE, particularly asymptomatic deep vein thrombosis (DVT), which can be readily detected on routine venography. For these reasons, this may be the ideal setting to evaluate the antithrombotic effects of a new anticoagulant as compared with that of an active comparator, such as a low-molecular weight heparin (LMWH) or a DOAC, and to investigate dose–response relationships. Once efficacy and safety data have been determined at various doses, other therapeutic indications can be assessed in subsequent trials. Early studies with one ASO (n = 1), mAbs (n = 2) and small molecules (n = 1) were conducted in patients undergoing arthroplasty, and provided proof of concept of their efficacy and safety.

The ASO IONIS-FXI has been tested in phase 2 trials in patients undergoing elective primary unilateral TKA (NCT01713361). In an open-label, parallel-group phase 2 trial (NCT01713361), 300 patients undergoing elective primary unilateral TKA were randomly allocated to treatment with IONIS-FXI (at the dosage of 200 mg or 300 mg, administered as three times per week during the first week of treatment, followed by weekly administrations) or enoxaparin (40 mg/day), starting 36 days before surgery. The trial was designed to assess the efficacy of IONIS-FXI in terms of reduction of VTE incidence (primary efficacy outcome), determined by mandatory bilateral venography or report of symptomatic events, while the principal safety outcome was major or clinically relevant non-major (CRNM) bleeding events. In the per-protocol analysis, the primary efficacy outcome occurred in 36 of 134 patients (27%) who received the 200 mg dose of the FXI-ASO compared with 21 of 69 patients (30%) who received enoxaparin, with similar results in the modified intention-to-treat analysis. The 200 mg regimen was non-inferior, and the 300 mg regimen proved superior to enoxaparin (P < 0.001). Regarding safety, major or CRNM bleeding events occurred in 3, 3, and 8% of the patients in the three study groups, respectively. This study showed for the first time that reducing FXI levels in patients undergoing elective primary unilateral TKA is an effective and safe approach for VTE prevention.

Two mAbs, osocimab and abelacimab, have been tested for this therapeutic indication. In a randomized, adjudicator-blinded, phase 2 non-inferiority trial (FOXTROT trial, NCT03276143), 813 adult patients undergoing unilateral knee arthroplasty were randomized to receive single intravenous pre- or post-operative doses of osocimab (0.3, 0.6, 1.2 or 1.8 mg/kg) or subcutaneous enoxaparin (40 mg/day) or two daily doses of oral apixaban (2.5 mg twice daily) for at least 10 days or until venography. The primary efficacy outcome was VTE incidence between 10 and 13 days post-operatively, assessed by mandatory bilateral venography or confirmed symptomatic events, whereas the primary safety outcome was major or CRNM bleeding, assessed in the same time window. The primary outcome occurred in 23.7% of patients receiving 0.3 mg/kg, 15.7% receiving 0.6 mg/kg, 16.5% receiving 1.2 mg/kg, and 17.9% receiving 1.8 mg/kg of osocimab post-operatively; in 29.9% receiving 0.3 mg/kg and 11.3% receiving 1.8 mg/kg of osocimab pre-operatively; in 26.3% receiving enoxaparin, and 14.5% receiving apixaban. The 0.6, 1.2 and 1.8 mg/kg osocimab dosages given post-operatively resulted non-inferior to enoxaparin, while the pre-operative dose of 1.8 mg/kg met criteria for superiority compared with enoxaparin with a risk difference of 15.1%. Regarding the safety outcome, major
<table>
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<tr>
<th>Compound/Company</th>
<th>Indication</th>
<th>Clinical trial</th>
<th>N. patients</th>
<th>Interventions</th>
<th>Efficacy data</th>
<th>Safety data</th>
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<td>Osocimab/Bayer</td>
<td>Post-operative (TKA)</td>
<td>FOXTROT trial, NCT03276143</td>
<td>813</td>
<td>Pre- or post-operative doses of osocimab (0.3, 0.6, 1.2 or 1.8 mg/kg, i.v.) or enoxaparin (40 mg/day s.c.) or apixaban (2.5 mg twice daily, oral) for at least 10 days or until venography</td>
<td>Primary outcome (VTE incidence between 10–13 days post-operatively, assessed at bilateral venography or symptomatic events): 24% in patients on 0.3 mg/kg, 16% receiving 0.6 mg/kg, 17% receiving 1.2 mg/kg, and 18% receiving 1.8 mg/kg of osocimab post-operatively; 30% in 0.3 mg/kg and 11% in 1.8 mg/kg of osocimab pre-operatively; 26% in enoxaparin; 15% in apixaban</td>
<td>Major or clinically relevant non-major bleeding events: 5% in osocimab, 6% in enoxaparin, and 2% in apixaban</td>
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<td></td>
<td>ESRD</td>
<td>CONVERT, NCT04523220</td>
<td>686</td>
<td>Osocimab (105 or 210 mg single s.c. loading dose, followed by 52.5 or 105 mg monthly doses) or placebo</td>
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<td>Abelacimab/Anthos Therapeutics</td>
<td>Post-operative (TKA)</td>
<td>ANT-005 TKA, EudraCT number 2019-003756-37</td>
<td>412</td>
<td>Abelacimab (30 mg, 75 mg, or 150 mg, single i.v. post-operative dose) or enoxaparin (40 mg/day s.c.)</td>
<td>VTE incidence (assessed by unilateral venography or symptomatic events): 13, 5 and 4% of patients in the 30, 75 and 150 mg abelacimab groups; 22% in enoxaparin</td>
<td>Major or clinically relevant non-major bleeding events: 2, 2, and 0% of patients in 30, 75 and 150 mg abelacimab; 0% in enoxaparin</td>
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<td>Atrial fibrillation</td>
<td>ANT-004, NCT04213807</td>
<td>18</td>
<td>Abelacimab (120 or 180mg, s.c. on Day 1 with two subsequent monthly injections for 3 months) or placebo</td>
<td>More than or equal to 90% inhibition of factor Xa: 33 and 57% in abelacimab 120 and 180mg, 0% in placebo</td>
<td>All-cause mortality and serious adverse events: 0% in all groups</td>
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<td>Atrial fibrillation</td>
<td>AZALEA-TIMI 71, NCT04753283</td>
<td>1200</td>
<td>Abelacimab (middle or high monthly dose, s.c.) or rivaroxaban (20 mg/day orally)</td>
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<td>Cancer (gastrointestinal/genitourinary)</td>
<td>MAGNOLIA trial, NCT05171075</td>
<td>1020</td>
<td>Abelacimab (150 mg iv., followed by monthly administration) or dalteparin (200 IU/kg/day followed by 150 IU/kg/day)</td>
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<td>Cancer</td>
<td>ASTER trial, NCT05171049</td>
<td>1655</td>
<td>Abelacimab (150 mg iv., followed by monthly administration) or apixaban (10 mg followed by 5 mg, orally twice daily)</td>
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<td>Xisomab 3G3/Aronora</td>
<td>ESRD on haemodialysis</td>
<td>NCT03612856</td>
<td>24</td>
<td>Xisomab 3G3 (0.25 or 0.5 mg/kg, single predialysis dose) or placebo</td>
<td>Less occlusive events requiring haemodialysis circuit exchange, lower levels of thrombin-antithrombin complexes, C-reactive protein, potassium and iron entrapment in the dialyzers, less blood accumulation within the dialyzers</td>
<td>No impaired haemostasis or other drug-related adverse events</td>
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<td>Cancer</td>
<td>NCT04465760</td>
<td>50</td>
<td>Xisomab 3G3 (i.v. or via catheter within 48 h of catheter placement; standard of care chemotherapy 2 days later)</td>
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<td>MK-2060/Merck Sharp &amp; Dohme</td>
<td>ESRD on haemodialysis</td>
<td>MK-2060-007 trial, NCT05027074</td>
<td>489</td>
<td>MK-2060 (low or high iv. dose, every other day during week 1, then once a week after week 1) vs. placebo</td>
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DVT, deep vein thrombosis; ESRD, end-stage renal disease; IU, international units; i.v., intravenous; s.c, subcutaneous; TKA, total knee arthroplasty; VTE, venous thromboembolism.
**Table 4**  Phase 2 trials on small molecules targeting FXI(a)

<table>
<thead>
<tr>
<th>Compound/ Company</th>
<th>Indication</th>
<th>Clinical trial</th>
<th>N. patients</th>
<th>Interventions</th>
<th>Efficacy data</th>
<th>Safety data</th>
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<tr>
<td>Milvexian/ Bristol-Myers Squibb—Janssen</td>
<td>Post-operative (TKA)</td>
<td>AXIOMATIC-TKR trial, NCT03891524</td>
<td>1242</td>
<td>Seven post-operative regimens of milvexian (25, 50, 100, or 200 mg twice daily or 25, 50, or 200 mg once daily, orally) or enoxaparin (40 mg/day, s.c.)</td>
<td>VTE (composite of asymptomatic DVT, confirmed symptomatic VTE, or death from any cause): 21, 11, 9 and 8% in milvexian 25, 50, 100 and 200 mg twice daily; 21, 24, 7% in milvexian 25, 50, and 200 mg once daily; 21% in enoxaparin</td>
<td>Major or clinically relevant non-major bleeding: 1% in milvexian, 2% in enoxaparin</td>
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<td>ESRD requiring haemodialysis</td>
<td>NCT03000673</td>
<td>32</td>
<td>Different sequences of: UFH intravenous infusion; milvexian 100 mg; milvexian 300 mg; enoxaparin (40 mg by s.c. injection)</td>
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<td>—</td>
<td>All-cause mortality and serious adverse events: 0% in all sequences</td>
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<td>Stroke</td>
<td>AXIOMATIC-SSP trial, NCT03766581</td>
<td>2366</td>
<td>Milvexian (+ aspirin and clopidogrel) or placebo (+ aspirin and clopidogrel)</td>
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<tr>
<td>Asundexian/Bayer</td>
<td>Atrial fibrillation</td>
<td>PACIFIC-AF, NCT04218266</td>
<td>753</td>
<td>Asundexian (20 to 50 mg/day, once daily orally) or apixaban (5 mg twice daily)</td>
<td>Inhibition of FXIa activity: 90% for asundexian 20 mg at peak concentrations, 94% for asundexian 50 mg</td>
<td>Ratios of incidence proportions for major or clinically relevant non-major bleeding events: 0.50 (90% CI: 0.14–1.68) for asundexian 20 mg, 0.16 (0.01–0.99) for asundexian 50 mg vs. apixaban.</td>
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<td>Acute heart attack</td>
<td>PACIFIC-AMI, NCT04304534</td>
<td>1592</td>
<td>Milvexian (low, medium or high dose, + aspirin +/- clopidogrel) or placebo (+ aspirin +/- clopidogrel)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Stroke</td>
<td>PACIFIC-STROKE, NCT04304508</td>
<td>1808</td>
<td>Asundexian (low, medium or high dose, + standard antiplatelet therapy) or placebo (+ standard antiplatelet therapy)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>NCT04510987</td>
<td>48</td>
<td>Asundexian (25mg, single oral dose)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>EP-7041/eXithera Pharmaceuticals</td>
<td>COVID-19 thromboprophylaxis</td>
<td>NCT05040776</td>
<td>90</td>
<td>EP-7041 (0.6 mg/kg/h i.v. or 1.0 mg/kg/h i.v. for the duration of the index hospitalization)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; ESRD, end-stage renal disease; IU, international units; i.v., intravenous; s.c, subcutaneous; TKA, total knee arthroplasty; VTE, venous thromboembolism.
or CRNM bleeding events occurred in 4.7% of patients on osocimab, 5.9% on enoxaparin, and 2% on apixaban.

In an open-label, parallel-group phase 2 trial (ANT-005 TKA, EudraCT number 2019-003756-37, 412 patients who were undergoing total knee arthroplasty were randomized to abelacimab (single intravenous post-operative dose of 30, 75, or 150 mg) or enoxaparin (40 mg/day subcutaneously). As in the other two previously mentioned trials, the primary efficacy and safety outcomes were VTE and major or CRNM bleeding up to 30 days after surgery, respectively. VTE occurred in 13, 5 and 4% of patients in the 30, 75 and 150 mg abelacimab groups, respectively, as compared with 22% in the enoxaparin group. The single intravenous 30 mg abelacimab regimen proved non-inferior to enoxaparin, and the 75 and 15 mg regimens were superior to enoxaparin (P < 0.001). Bleeding was infrequent, occurring in 2%, 2%, and 0% of patients in the three abelacimab groups as compared with 0% in the enoxaparin group.

The small molecule milvexian was tested in patients undergoing knee arthroplasty. In a parallel-group, phase 2 trial (AXIOMATIC-TKR trial), 1242 patients were randomly assigned to one of seven post-operative regimens of milvexian (25, 50, 100, or 200 mg twice daily or 25 mg, 50 mg, or 200 mg once daily, administered orally) or enoxaparin (40 mg/day, subcutaneously). The primary efficacy outcome was VTE, defined as a composite of asymptomatic DVT, confirmed symptomatic VTE, or death from any cause. Post-operative FXa inhibition with oral milvexian was effective for VTE prevention: VTE occurred in 21, 11, 9 and 8% of patients receiving milvexian 25, 50, 100 and 200 mg twice daily, respectively, and in 25, 24, 7% of those on 25, 50, and 200 mg once daily, as compared with 21% in patients taking enoxaparin. As for safety outcomes, bleeding of any severity occurred in 4% of patients taking milvexian and 4% taking enoxaparin, while major or CRNM bleeding occurred in 1 and 2%, respectively. Results from the ongoing phase 2 study of milvexian for secondary stroke prevention (AXIOMATIC-SSP) are expected soon.

In summary, the four anti-FXI agents evaluated in these phase 2 trials (the ASO IONIS-FXIRx, the mAbs osocimab and abelacimab, and the small-molecule milvexian) demonstrated potential to be more effective than enoxaparin in preventing VTE in patients undergoing total knee replacement (TKR), with low bleeding risk. Results are coherent with the biologically plausible expectation that FXI inhibition plays a more important role in thrombosis than haemostasis and supported further evaluation of these and other drugs that target factor XI in phase 3 randomized trials.

Prevention and treatment of cancer-associated venous thromboembolism

Cancer is associated with an increased risk of VTE, which represents a frequent cause of morbidity and mortality in cancer populations. DOACs are replacing LMWH as the preferred treatment for cancer-related VTE because they are at least as effective and avoid the need for daily injection. Regarding safety, a meta-analysis of four RCTs revealed that in cancer patients the risk of major bleeding was comparable to placebo and better than LMWH (RR: 1.31 (95% CI: 0.83–2.08)). However, still around 4% of patients on apixaban developed major gastrointestinal or non-gastrointestinal bleeding.

A phase 2 trial is ongoing to assess the efficacy and safety of the recombinant humanized mAb xismab 3G3 for the prevention of catheter-associated thrombosis in patients with cancer receiving chemotherapy (NCT04465760). Moreover, two phase 2 trials are comparing the mAb abelacimab with dalteparin for VTE prevention in gastrointestinal/genitourinary cancer (MAGNOLIA trial, NCT05171075) and with apixaban in the treatment of cancer-associated VTE (ASTER trial, NCT05171049), respectively.

Prevention of cardiovascular events in patients with end-stage renal disease or undergoing haemodialysis

Chronic kidney disease is increasingly prevalent, particularly among the elderly, and is a strong and independent risk factor for cardio- and cerebro-vascular events. Moreover, patients with kidney disease are at higher risk of bleeding during anticoagulant treatment than patients with normal renal function, and there is uncertainty about the role of DOACs in patients with ESRD requiring dialysis. ASOs and mAbs are not excreted by the kidney and are not removed by dialysis, making them attractive candidates for use in patients with advanced kidney disease. Small molecule inhibitors are minimally cleared by the kidneys (8–20%) and are unlikely to be cleared by the kidneys because they are highly protein bound.

The ASO IONIS-FXIRx has been tested in phase 2 trials in patients with ESRD on haemodialysis (NCT02553889; NCT03358030 – EMERALD trial). Fesomersen is currently under investigation in a further phase 2 trial on ESRD patients requiring haemodialysis (NCT04534114 – RE-THINc ESRD trial).

Two other randomized, double-blind, placebo-controlled phase 2 trials have been conducted to assess safety, pharmacokinetics, and pharmacodynamics of multiple doses of the ASO IONIS-FXIRx (200–300 mg, administered subcutaneously) in patients with ESRD on haemodialysis (NCT02553889; EMERALD trial, NCT03358030). Preliminary results indicate that haemodialysis has no effect on IONIS-FXIRx pharmacokinetics and tolerability, and that the treatment effectively reduces dialysis circuit clotting events. The phase-2b RE-THINc trial on fesomersen in ESRD has recently been completed (NCT04534114). The study included 307 patients with ESRD on haemodialysis who were randomized to three different regimens of fesomersen (40 mg, 80 mg or 120 mg administered subcutaneously every 4 weeks for up to 48 weeks) or placebo. Although full results have not been released yet, preliminary reports indicate positive topline results: fesomersen achieved the primary safety outcome of no increase in the risk of major bleeding and clinically relevant non-major bleeding as compared to placebo, resulting safe and well-tolerated.

The mAb osocimab, is under investigation in a phase 2 trial in patients with kidney failure requiring haemodialysis (CONVERT trial – NCT04523220). This trial has been completed, but results have not been released yet. A phase 2, randomized, double-blind, placebo-controlled trial was conducted to assess the safety and efficacy of a single dose of xismab 3G (0.25 or 0.5 mg/kg), administered at the beginning of a regular haemodialysis procedure, in ESRD patients on chronic haemodialysis (NCT03612856). The results from the 24 patients included in this trial indicate that xismab 3G administration was not associated with impaired haemostasis or other drug-related adverse events. Occulsive events in the haemodialysis circuit were less frequent in the xismab 3G group than in the placebo group, and levels of thrombin-antithrombin complexes and C-reactive protein were lower after compared with before xismab 3G administration.

In a phase 1 study, the safety and tolerability of asundexian (25 mg) has been investigated in patients with renal impairment, including those on haemodialysis (NCT04510987); results are still unpublished.
phase 1/phase 2 study assessed safety and tolerability of single oral doses of the small molecule milvexian as compared with enoxaparin or unfractionated heparin in patients with ESRD on chronic haemodialysis (NCT03000673), but results are unpublished.

**Stroke prevention in atrial fibrillation**

Progressive increase in the global prevalence of atrial fibrillation highlights the need for effective and safe pharmacological therapies for stroke prevention in these patients. **DOACs** are commonly used in this condition, and much safer than VKAs as to the risk of intracranial haemorrhage, but the residual risk of cardio- and cerebro-vascular events on the one hand, and the occurrence of intra- and extracranial bleeding events even under DOACs on the other have prompted research for alternative anti-coagulant agents, and, namely, for FXI inhibitors.

A multicentre, randomised, subject, and investigator-blinded, placebo-controlled, parallel-group, multiple ascending dose-ranging phase 2 trial has thus been conducted to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of the mAb abelacimab in patients with atrial fibrillation or flutter at low risk of thromboembolic stroke or peripheral embolism (ANT-004, NCT04213807). Abelacimab (120 or 180 mg) was administered subcutaneously on Day 1 with two subsequent monthly injections to six and seven patients, respectively, as compared with five receiving placebo. The study has provided encouragement for the much larger safety and tolerability of abelacimab (MAA868) vs. rivaroxaban in patients with atrial fibrillation (AZALEA-TIMI 71, NCT04755283), in which 1200 participants are planned to be randomized to two blinded doses of abelacimab relative to open-label rivaroxaban on the rate of major or CRNM bleeding events in patients with atrial fibrillation who are at moderate-to-high risk of stroke. The study is planned to end in January 2023.

The two most prominent developments are now, however, been carried out with the small molecules milvexian and asundexian. After the favourable completion of the AXIOMATIC-TKR for post-operative VTE prevention in patients undergoing elective TKR surgery, milvexian investigation is now being planned in a large phase 3 atrial fibrillation study. Another multicentre, randomized, active comparator-controlled, double-blind, parallel-group, dose-finding phase 2 study has been conducted to compare the safety of asundexian (20–50 mg/day, administered orally) to apixaban in patients with atrial fibrillation (NCT04218266, PACIFIC-AF). The purpose of this study was to find the best dose of the drug also comparing the safety of the study drug to the DOAC apixaban in patients with atrial fibrillation. In this study, in 753 patients included in the analysis (249 receiving asundexian 20 mg, 254 receiving asundexian 50 mg, and 250 receiving apixaban), asundexian 20 mg resulted in 81% inhibition of FXa activity at trough concentrations and 90% inhibition at peak concentrations; asundexian 50 mg resulted in 92% inhibition at trough concentrations and 94% inhibition at peak concentrations. Ratios of incidence proportions for the primary endpoint—the composite of major or CRNM bleeding according to International Society on Thrombosis and Haemostasis criteria—were 0.50 (90% CI: 0.14–1.68) for asundexian 20 mg (three events), 0.16 (0.01–0.99) for asundexian 50 mg (one event), and 0.33 (0.09–0.97) for pooled asundexian doses (four events) vs. apixaban (six events). The rate of any adverse event occurring was similar in the three treatment groups: 118 (47%) with asundexian 20 mg, 120 (47%) with asundexian 50 mg, and 122 (49%) with apixaban. In the now starting OCEANIC-AF trial asundexian 50 mg OD will be compared with apixaban (5 mg BID per-label reduced to 2.5 mg BID) in ~15,000 patients with atrial fibrillation, aimed at demonstrating superiority over both ischaemic and bleeding events for the former over the latter.

**Secondary prophylaxis of non-cardioembolic stroke**

The AXIOMATIC-SSP study (NCT03766581) is a global, phase 2, randomized, double-blind, placebo-controlled, dose-ranging study of milvexian for the secondary prevention of new ischaemic stroke or newly detected brain infarction in patients following acute non-haemorrhagic stroke or a transient ischaemic attack who are treated with standard antplatelet therapy, including 1 month of dual antplatelet therapy (DAPT) followed by long-term aspirin. The purpose of this clinical study is to determine whether the addition of an oral anti-FXI agent to aspirin and clopidogrel is more effective than the standard therapy in secondary stroke prevention. The trial is currently ongoing and will give key information on the safety and efficacy of milvexian in conjunction with dual and single antplatelet therapy. The results from this trial will also help identifying the optimal doses that can be carried forward into subsequent phase 3 programmes in this clinical condition.

PACIFIC-STROKE (NCT04304508) is a global phase 2 randomized double-blind, placebo-controlled, dose-ranging study of asundexian for secondary prevention of new ischaemic stroke in about 1800 patients following acute non-haemorrhagic stroke or a transient ischaemic attack who are treated with standard antplatelet therapy. Asundexian was given in the same three doses as in PACIFIC-AMI and compared with matching placebo. All participants received routine antplatelet therapy. The primary endpoint was the composite of symptomatic ischaemic stroke or covert brain infarct detected by magnetic resonance imaging. Asundexian did not reduce the composite of covert brain infarction or ischaemic stroke and did not increase the composite of major or clinically relevant non-major bleeding compared with placebo in patients with acute, non-cardioembolic ischaemic stroke.

The results of a phase 2 dose-finding study of milvexian in patients with recent stroke have also recently been presented, but they are not yet published. The AXIOMATIC secondary stroke prevention (SSP) trial compared five doses of milvexian with placebo in 2,366 patients with recent mild stroke or high-risk TIA who were receiving routine antplatelet therapy with the combination of aspirin and clopidogrel. There was no evidence of a dose-response for the primary endpoint, a composite of new ischaemic stroke or new covert brain infarction detected by magnetic resonance imaging, but doses of milvexian except the highest were associated with fewer symptomatic ischaemic strokes. The three highest doses of milvexian were associated with more major bleeds than placebo, but the differences for both symptomatic stroke and major bleeding were not statistically significant. The pattern of reduction in symptomatic stroke is similar to that seen with asundexian in the PACIFIC-stroke study (https://www.phri.ca/research/axiomatic-ssp/).

**Secondary cardiovascular prevention after a myocardial infarction**

The standard of care in patients with acute coronary syndrome (ACS) is DAPT with aspirin and a P2Y12 receptor inhibitor. However, the risk of ischaemic recurrences in these patients remains high despite DAPT. The persistence of thrombin generation after an ACS may contribute to these events, suggesting the need for long-term anticoagulation in these patients. Various DOACs have been tested in ACS patients, but only rivaroxaban successfully completed phase 3 clinical investigation and was approved for clinical use in most parts of the world for patients with ACS. In the ATLAS ACS 2-TIMI 51 trial on patients with a recent ACS, the use of rivaroxaban in association with aspirin
and an antiplatelet agent reduced the risk of the composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke. However, the combination of rivaroxaban and DAPT was associated with a higher risk of major bleeding and intracranial haemorrhage, though not of fatal bleeding, thus suggesting the need of identifying safer therapeutic alternatives.

To date, one phase 2 trial has just been completed to assess the proper dose and safety of the anti-FXI small molecule asundexian in >1500 patients following an acute myocardial infarction (PACIFIC-AMI, NCT04304534). The results of this phase 2 trial have been recently presented and published. Three doses of asundexian (50 mg daily (n = 402), 20 mg daily (n = 401), 10 mg daily (n = 397), or matching placebo (n = 401) were compared for safety and efficacy in patients with spontaneous acute myocardial infarction (AMI, 52% being ST segment elevation AMI) treated with PCI and with dual antiplatelet therapy (DAPT). 89% of whom receiving ticagrelor or prasugrel. Mean patient age was 68 years. Follow-up duration was 6 months.

The primary safety outcome, Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding at 6 months for asundexian 50 mg daily vs asundexian 20 mg daily vs asundexian 10 mg daily vs placebo, was: 10.5% vs 8.1% vs 7.6% vs 9.0% (all asundexian vs placebo p >0.05). Two patients with asundexian 50 mg and one patient with placebo had intracerebral hemorrhage (ICH). Primary efficacy outcome (cardiovascular death, MI, stroke, stent thrombosis), as well as its individual components, occurred similarly in the 4 groups (all asundexian vs placebo p >0.05). Thus, asundexian in addition to DAPT among patients undergoing PCI for AMI did not increase bleeding with any of the doses studied compared with placebo, although there appeared to be stepwise increase with higher doses. Ischemic events were infrequent, but also no different between asundexian and placebo. Measured factor Xla levels were also reduced in a dose-related fashion with >90% reduction compared with baseline with asundexian 50 mg daily 1. Based on this trial, asundexian 50 mg daily will be tested in a cardiovascular outcomes (phase 3) trial (OCEANIC-AMI) among patients with AMI, aimed at demonstrating a >20% reduction of cardiovascular death, myocardial infarction and stroke in such patients on top of DAPT, with no relevant impact on bleeding.

Thromboprophylaxis in COVID-19 patients

To date, only one agent, the small molecule EP-7041, is in active development for COVID-19 patients who require care in an intensive care unit, regardless of whether or not mechanical ventilation is in use or is anticipated (NCT05040776).

Prevention of central venous catheter thrombosis

Pre-clinical data support the concept that reducing FXIIa or FXIa generation attenuates catheter-associated clotting. In rabbit models, catheters coated with corn trypsin inhibitor, a specific inhibitor of FXIIa, remained patent longer than uncoated catheters when implanted in the jugular veins of rabbits. Likewise, in the same animal model, knockdown of FXII or FXI with specific ASOs prolonged catheter patency, whereas knockdown of FVII did not. Based on this pre-clinical evidence, it can be assumed that FXI inhibitors might find a place also in the prevention of central venous catheter thrombosis, although to date no clinical study has assessed the efficacy and safety of anti-FXI in this setting. As mentioned previously, a phase 2 single-arm clinical trial with xisomab 3G3 is ongoing for the prevention of catheter-associated thrombosis in patients with cancer receiving chemotherapy (NCT04465760).

Other potential future indications

Prophylaxis of clotting in extracorporeal membrane oxygenation circuits

The use of extracorporeal membrane oxygenation (ECMO) has become more common over the last years, also due to the COVID-19 pandemic. However, the use of ECMO is associated with frequent complications, including vascular injury from cannula placement, coagulopathy—with both thromboembolic and haemorrhagic sequelae—, lung injury, stroke, infection, and heparin-induced thrombocytopenia. Current antithrombotic prophylaxis in ECMO patients is limited by the risk of both thrombotic and bleeding complications. The promise of improved safety makes inhibition of FXI an attractive option in these patients.

Prevention of cardiac device-triggered thromboembolic events

Treatment options for patients with advanced heart failure has remarkably changed after the introduction of left ventricular assist devices (LVADs), both in patients awaiting transplant and in transplant-ineligible patients. However, LVAD use requires a careful balance of the risks of thrombotic and bleeding complications, but to date the optimal anticoagulant regimen in these patients is far from being clearly defined. Of currently available anticoagulant treatments, DOACs seem to be inferior to VKAs in preventing thrombosis in LVAD patients, probably due to the fact that thrombus formation is here primarily induced by activation of the contact pathway. On these biological bases, anti-FXI agents may be particularly effective for thrombosis prevention in such a setting, while also displaying a better safety profile, reducing the risk of bleeding complications. Similar considerations can be made for patients with mechanical heart valves, for whom the standard of care is represented by VKAs, given the negative results of the Re-ALIGN study with dabigatran. However, to date, it is still unclear whether clinical trials will be actually planned in this therapeutic field.

Prevention of thrombosis in high-risk antiphospholipid syndrome patients

As extensively described above, the use of FXI inhibitors in clinical conditions where artificial surfaces are involved is based on the solid rationale that upstream inhibition of the FXIIa-induced intrinsic pathway activation is crucial for VTE prevention in these settings. Conversely, the potential role of FXI inhibitors in other prothrombotic conditions, such as in the antiphospholipid syndrome (APS), is still uncertain. The APS is an immune-mediated condition characterized by thrombotic events and/or by obstetric complications. APS patients who carry a triple positivity for lupus anticoagulant, anticardiolipin and anti-β2-glycoprotein I antibodies are included among special populations in which DOAC use is currently contraindicated. Indeed, subsequent to studies reporting higher rates of recurrent thrombosis with rivaroxaban compared with VKAs, VKAs are here still considered the standard of care, despite the high risk of bleeding and the well-known difficulties related to treatment management. Thus, it is reasonable that FXI inhibitors will be tested in this condition, as the lower risk of bleeding connected with their use might allow to test incremental dosages and to guarantee an easier management, also considering the prevailing young age of these patients. However, as a warning, FXI inhibitors cannot reduce prothrombin levels, which is considered one of the potential antithrombotic mechanisms of VKAs in APS.
Conclusions and perspectives

Despite important safety and convenience advantages of DOACs, the risk of bleeding remains an important barrier to the use of long-term oral anticoagulant therapy. Furthermore, DOACs remain contraindicated for patients with mechanical heart valves and triple-positive APS, highlighting the need for new approaches for the prevention and treatment of thrombosis. Proof of concept for targeting coagulation FXI comes from the results of early-stage randomized trials, but definitive evidence for superior safety and efficacy of this new therapeutic strategy awaits the results of phase 3 trials that are currently in advanced stages of planning and conduct. The results of these trials will also clarify whether there are meaningful differences between interventions that lower FXI antigen levels and those that target FXIa. The biggest test for drugs that target FXI is likely to come from settings where thrombus formation results from exposure of blood to artificial surfaces, such as patients with mechanical heart valves for whom VKAs are still the only approved therapy, and those at very high risk of bleeding, including patients with advanced kidney disease undergoing haemodialysis. Successful evaluation for these and other indications will usher in yet another new era in anticoagulant therapy. Finally, as with any new class of drugs, safety issues may emerge and will need to be tackled. These include, besides the mentioned side effects of mAbs and ASOs, the potential difficulty in antagonizing FXI inhibitors with FXI concentrates, which can be thrombogenic, or with prothrombin complex concentrates, which may not be sufficiently effective. Clinical studies and registries will define the clinical relevance of such concerns.

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Data availability

No original data here provided. Summary data available upon reasonable requests.

References


