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Factor XI inhibitors — a breakthrough in prevention and treatment of thromboembolic disorders

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Summary

Available pharmacological antithrombotic prophylaxis is associated with a low but noticeable risk of bleeding. Hence, there is an ongoing search for effective antithrombotic medications which do not significantly increase bleeding risk. Factor XI inhibitors seem to fulfil these requirements. Results of presently available randomized clinical trials on the use of factor XI inhibitors in venous thromboembolism prophylaxis and prevention of arterial thrombosis are presented.

Key words: antithrombotic prophylaxis, venous thromboembolism, factor XI inhibitors, arterial thrombosis, knee replacement therapy, hip replacement therapy

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Anticoagulant drugs are the mainstay of management of venous and arterial thrombosis. For almost 70 years acenocoumarol or warfarin — oral vitamin K antagonists (VKAs) — have been the drugs of choice for long-term prophylaxis and management of thromboembolic complications. The VKA therapy does however have some limitations related to their pharmacodynamics and pharmacokinetics , as well as to numerous drug-drug and drug-food interactions. Hence the need for frequent monitoring of the international normalizing ratio (INR) to keep their anticoagulant effect in the therapeutic range. Although INR control reduces the risk of severe bleeding, the patients on Vitamin K antagonists (VKAs) are still at approximately 10-fold higher risk of intracranial bleeding than the patients not receiving anticoagulants [1]. VKAs inhibit blood coagulation process at various steps of the coagulation cascade by impairing the synthesis of vitamin K-dependent coagulation factors, i.e. prothrombin, factors VII, IX and X.

It was only 10 years ago or so that easy-to-use direct oral anticoagulants (DOACs) such as thrombin inhibitors (dabigatran) or activated factor X inhibitors (rivaroxaban, apixaban, edoxaban) were registered and introduced in the European Union. Currently, DOACs which directly target specific coagulation factors are preferred agents both in the therapy of venous thromboembolism (VTE) [2] as well as in the prevention of ischemic stroke in patients with non-valvular atrial fibrillation [3]. The advantage of DOACs over VKA is the convenience of use, higher therapeutic efficacy and, above all 40% reduction of major bleeding risk including a 50% reduction in intracranial hemorrhage [3, 4]. Although clinically effective, easy to use, with no need for INR monitoring, the DOACs are nevertheless associated with an increased bleeding risk, mostly from the gastrointestinal tract [3, 4].

Underway is therefore, the search for an anticoagulant that would prevent pathological thrombotic episodes while sparing physiological

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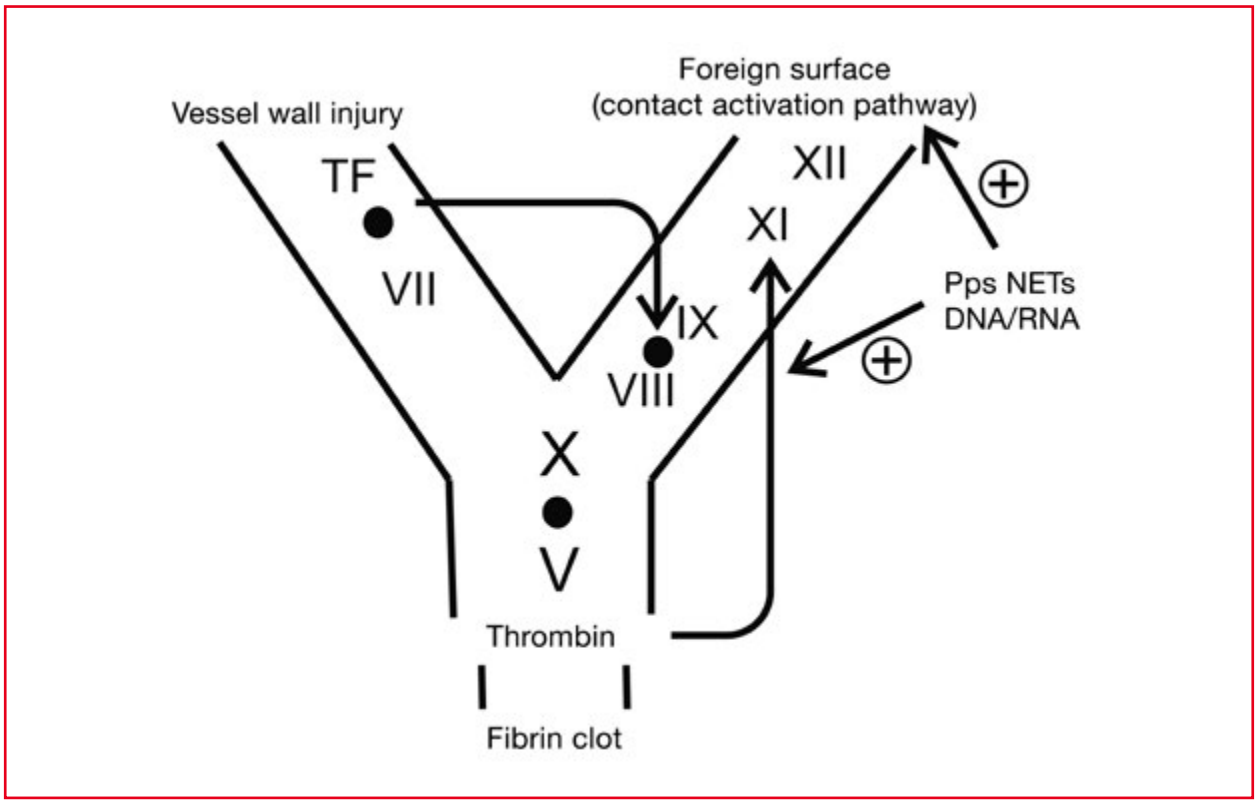

Figure 1. Factor XI in the clotting cascade

hemostasis [5]. Currently, it may seem that the answer here are factor XI inhibitors.

Once the vessel wall injury occurs, hemostasis is initiated with factor VII, or its activated form (VIIa) binding to extravascular tissue factor (TF) exposed at the site of injury. The FVIIa•TF complex converts FX to FXa which together with factor V (FX•FV complex) converts prothrombin to thrombin. In consequence, thrombin converts circulating fibrinogen into a fibrin clot.

Along this pathway, previously referred to as the extrinsic (coagulation) pathway, bleeding from the injured vessel is stopped by formation of a hemostatic plug (clot) within the vessel wall and the immediate extravascular environment. Physiological hemostasis is thus ensured (Fig. 1).

Simultaneously the FVIIa•TF complex activates factor IX, which together with FVIII (FIX•FVIII complex) further activates FX leading to amplification of thrombin formation. Generated thrombin augments its own synthesis by activating factor XI, which in turn has the ability to activate factor IX and thus maintains further thrombin formation [6]. This pathway of sustained thrombin generation is probably only auxiliary to physiological haemostasis, as the congenital factor XI deficiency is associated with a slight variable mucosal bleeding tendency which usually follows minor surgical procedures or major trauma [7].

Factor XI is one of the constituents of the contact pathway of blood coagulation cascade together with factor XII, prekallikrein and high-molecular-weight kininogen. Along this pathway, in a reaction enhanced by anionic polymers (DNA and RNA, neutrophil extracellular traps [NETs] or inorganic polyphosphates included), blood in contact with artificial surfaces leads to mutual activation of factor XII and prekallikrein.

Factor XII then activates factor XI, which leads to thrombin generation along the extrinsic coagulation pathway [8] (Fig. 1). Hence the hypothesis that by inhibiting factor XI, it may be possible to uncouple and leave intact physiological hemostasis (extrinsic and common pathway), and at the same time to impair the processes of pathological clot formation (thrombosis) [6]. The desired end result would be attenuation of pathological thrombosis without disruption hemostasis/at no higher risk for bleeding. The above is perceived as the "Holy Grail" of antithrombotic prophylaxis.

To date, a number of molecules have been synthesized and developed which inhibit factor XI along different pathways. They can be classified as follows:

1. Antisense oligonucleotides — for subcutaneous administration (at weekly or monthly intervals) which inhibit factor XI synthesis and reduce factor XI level in blood. As of the end of October 2022 the trials reached the clinical phase for IONIS-FXIRX and Fesomersen;
2. Monoclonal antibodies — for intravenous or subcutaneous administration (at monthly intervals) which bind factor XI; used presently in clinical trials: Osocimab, Abelacimab Xisomab 3G3 (the latter inhibits factor XI activation through factor XIIa);
3. Small molecule inhibitors — for oral administration (daily) which inhibit the factor XIa active center; so far used in clinical trials: Milvexian, Asudexian.
4. Natural inhibitors — isolated from living organisms — nematodes, ticks, bats, and snakes — for parenteral use; inhibit either factor XI, or the entire contact pathway. Not yet in clinical trials.

This list does not cover all options as there are also several other compounds in the early stages of in vitro or in vivo assessment (unlisted here).

So far, only phase 2 human randomized clinical trials have been completed. As is usually the case, the first studies focus on antithrombotic prophylaxis in patients at particular risk for venous thromboembolism (VTE). This group includes mainly those patients who are scheduled for elective hip or knee replacement.

Hence, the first Phase II study to determine the efficacy and safety profile as well as the optimal dose of the antisense oligonucleotide to inhibit factor XI synthesis was performed in a group of patients scheduled for elective knee replacement. Enoxaparin was the control drug [9]. Antisense oligonucleotide was administered subcutaneously beginning with the 36th day prior to procedure and then continued until the 3rd post-operative day. Enoxaparin was usually administered 6 to 8 hours before surgery and was continued for at least 8 days after surgery. Depending on the drug dose, the post-operation factor XI level was 3–4 times lower than in control patients (who received enoxaparin). Lower dose antisense oligonucleotide was as effective for VTE prevention as enoxaparin, while the higher dose proved more effective (4% of VTE episodes against 30% after enoxparin; bleeding frequency in 3% and 8% of patients, respectively). Venograms were performed for all the patients thus the high frequency of detected VTE episodes. The major conclusions state that firstly, factor XI seems to play an important role in the development of postoperative VTE episodes, and secondly, inhibition of factor XI synthesis in patients subjected to knee replacement effectively prevents the occurrence of VTE episodes. With this procedure the bleeding risk is low.

In 2020 and 2021, the results of three consecutive trials were published and these also referred to patients subjected to knee replacement. The trials focused on the effects of osocimab, abelacimab and milvexian (respectively) [10–12]. The conclusion from recent meta-analysis of the available study data is that compared to low molecular weight heparin (LMWH), factor XI inhibitors reduce the risk of symptomatic and asymptomatic VTE by 50% [odds ratio (OR) 0.50; 95% confidence interval (CI) 0.36–0.69] and that of bleeding risk by approx. 55%. For clinically significant bleeding, the OR was 0.41 (95% CI 0.22–0.75). The risk for VTE episodes in the study patients treated with LMWH was estimated at 23.6%, and that for major or clinically significant bleeding at 3.2% [13].

It seems therefore that factor XI inhibition along the intrinsic coagulation pathway, may prevent VTE episodes at no significant increase in bleeding risk. At least it is true for patients who undergo joint replacement. This may be explained by the fact that the extrinsic and common coagulation pathways remain intact (Fig. 1).

The efficacy of factor XI inhibitors in the prevention of VTE episodes stimulated research on the use of these inhibitors in the prevention of thrombotic episodes in the cardiovascular system, mainly ischemic stroke, and recurrence of ischemic episodes in patients after myocardial infarction. Up to date, literature is quite limited in this respect. Some studies are in progress but the results are still unavailable. Results of several studies have however been published this year and they deserve to be discussed.

In a phase II trial PACIFIC-AF of 755 patients with atrial fibrillation, the safety profile of asundexian (20 or 50 mg) — an oral small-molecule factor XI inhibitor — was compared with apixaban (2 × 5 mg) [14]. The inhibition of factor XIa activity was shown to be dose-dependent (20 and 50 mg, dose resulted in 90% and 92% reduction of FXI activity, respectively). Markedly fewer severe, clinically significant bleeding were reported with the tested drug (for the highest 50 mg dose of asundexian — OR 0.16; 95% CI 0.01–0.99).

The PACIFIC-Stroke trial focused on the efficacy and safety profile of 3 doses of asundexian compared to placebo (all patients were on standard antiplatelet therapy) as part of the secondary pre-

vention of ischemic stroke in 2000 patients who experienced such stroke or a transient ischemic episode [15]. None of the asundexian doses contributed to lower recurrence frequency of cerebral episodes (either symptomatic or magnetic resonance detected), nor did it significantly increase the bleeding risk. A secondary analysis however revealed a lower frequency of cerebral events in a small subgroup of patients with symptomatic ischemic stroke.

There have also appeared reports of a similar trial — AXIOMATC (results yet unpublished) describing the use of milvexian which reduced the frequency of symptomatic ischemic stroke episodes, at no significantly higher bleeding frequency [16].

In the era of intracoronary interventions the recurrence risk for ischemic episodes in patients with acute myocardial infarction is still estimated at about 7% during 3 years despite dual antiplatelet therapy. Low doses of rivaroxaban added to antiplatelet drugs may reduce the risk, but at the cost of higher bleeding risk [17]. An attempt was therefore made to use asundexian — a factor XI inhibitor in this setting. In the PACIFIC-AMI trial, 1600 patients after acute myocardial infarction and treated with dual antiplatelet therapy were administered asundexian at 3 different doses or placebo [18]. Although asundexian effectively inhibited FXIa activity (at a dose of 50 mg > 90%) at no higher risk of bleeding, there was no significant reduction in the frequency of the composite endpoint (cardiovascular death, myocardial infarction, stroke, or stent thrombosis).

Thus, in contrast to the earlier described favorable effect of factor XI inhibitors for prevention of VTE in patients undergoing joint replacement, the role of these compounds for prevention of thromboembolic events in the arterial system does not seem as beneficial (according to the phase II trials available so far). Perhaps, as suggested for secondary prevention in acute myocardial infarction, further research should focus on patients at the highest risk of recurrence and with the highest doses of oral FXIa inhibitors tested [19].

In order to definitively determine the place of factor XI inhibitors in the prevention and treatment of venous thrombosis, we have to wait for phase III trials in the already discussed clinical situations. Important would be also the results of the ongoing trials for other indications: e.g., prophylaxis and antithrombotic treatment of patients with chronic kidney diseases, cancer-related VTE prophylaxis, prevention of thrombosis in foreign surface-containing circulatory external devices (ECMO, hemodialysis), or prevention of thromboembolic complications in non-valvular atrial fibrillation [16]. No doubt, however, factor XI inhibitors and perhaps also inhibitors of other constituents of the contact coagulation pathway are to be perceived as new, promising alternatives to the management and prevention of thrombotic disorders.

Conflict of interest: none declared

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