Factor XI inhibitors: a new option for the prevention and treatment of cancer-associated thrombosis

Marcello Di Nisio,[1] Matteo Candeloro,[2] Nicola Potere,[1] Ettore Porreca,[2] Jeffrey I. Weitz[3,4]

[1]Department of Medicine and Ageing Sciences, University "G. d'Annunzio", Chieti-Pescara, Italy; [2]Department of Innovative Technologies in Medicine and Dentistry, "G. d'Annunzio" University, Chieti-Pescara, Italy; [3]Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada; [4]Department of Medicine and Department of Biochemistry and Biomedical Sciences, McMaster University, Hamilton, ON, Canada

ABSTRACT

Venous thromboembolism (VTE) is a relatively common complication in cancer patients with potentially dire consequences. Anticoagulants are the mainstay of treatment of cancer-associated VTE. The anticoagulants most often used are low-molecular-weight heparin (LMWH) and direct oral factor (F) Xa inhibitors, which include apixaban, edoxaban, and rivaroxaban. Most guidelines recommend primary VTE prophylaxis with LMWH, apixaban, or rivaroxaban after abdominal or pelvic cancer surgery, or in high-risk ambulatory cancer patients. Both oral FXa inhibitors and LMWH have limitations. LMWH requires daily subcutaneous injections, and because of its renal clearance, its use may be problematic in patients with severe kidney disease. The risk of bleeding with oral FXa inhibitors may be higher than with LMWH in patients with intraluminal gastrointestinal or genitourinary cancers. Other problems with oral FXa inhibitors include potential drug-drug interactions and dosing issues in patients with thrombocytopenia or severe kidney or liver disease. Therefore, there remains a need for convenient and safer anticoagulants for VTE treatment in cancer patients. FXI has emerged as a potentially safer target for anticoagulants than FXa because FXI is essential for thrombosis, but mostly dispensable for hemostasis. This review summarizes the currently available therapeutic options for cancer-associated VTE, highlights knowledge gaps, and discusses the potential of FXI inhibitors to address key unmet clinical needs in this vulnerable patient population.

Correspondence: Marcello Di Nisio, Department of Medicine and Ageing Sciences, University "G. d'Annunzio", Chieti-Pescara, Italy. E-mail: mdinisio@unich.it

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is relatively common in patients with cancer.[1] Over the last few decades, the incidence of VTE has remained relatively stable in the general population, whereas it has progressively increased in cancer patients.[2] In a large population-based study, the 6-month VTE risk in patients with cancer was 12-fold higher than that in subjects without cancer, and up to 23-fold higher among those receiving chemotherapy or targeted treatments.[2]

Cancer-associated thrombosis (CAT) represents the second most common cause of death in cancer patients after tumor progression,[1] and it's associated with substantial morbidity including repeated hospitalizations and delays or interruptions in potentially curative cancer-directed treatments.[3,4] CAT is a distressing experience for patients and their relatives, increasing the psychological burden on vulnerable individuals already overwhelmed by the cancer diagnosis and its treatment.[4,5] Treatment of VTE in cancer patients is challenging because of their heightened risk of recurrence and bleeding compared with patients without cancer.[6,7] Both recurrent VTE and bleeding are associated with poorer quality of life, deferral or disruption of cancer treatments, and increased healthcare costs.[8]

The purpose of this review is to summarize the current therapeutic options for CAT, highlight current knowledge gaps, and explain how the new generation of factor (F) XI inhibitors may address unmet clinical needs.

Current treatment of cancer-associated thrombosis

Low molecular-weight heparin (LMWH) and direct oral FXa inhibitors, which include apixaban, edoxaban, and rivaroxaban are the current standards of care for CAT. In patients with CAT, studies have shown that oral FXa inhibitors are at least as effective as LMWH, and associated with a non-significant increase in major bleeding.[9-14] Recent clinical guidelines suggest oral FXa inhibitors as an alternative to LMWH for most patients with CAT.[15-18] Oral FXa inhibitors are more convenient to administer than LMWH, but their use may be problematic in patients with impaired gastrointestinal absorption secondary to vomiting, diarrhea, or upper gastrointestinal surgery. Patients with gastroesophageal or genitourinary cancers, especially those with unresected luminal tumors, had a higher risk of bleeding with edoxaban or rivaroxaban than with dalteparin.[9,10,19,20] Although the risk of bleeding with apixaban was similar to that with dalteparin,[13] recent guidelines suggest the use of LMWH rather than oral FXa inhibitors in patients with unresected gastrointestinal or genitourinary cancers.[15-18] All oral FXa inhibitors are substrates of P-glycoprotein, and apixaban and rivaroxaban are metabolized by cytochrome (CYP) 3A4. Consequently, the concomitant use of drugs that affect these pathways could influence drug concentrations and increase the risk of bleeding or thrombotic complications.[21,22] Most guidelines endorse the preferential use of LMWH in cancer patients receiving strong inducers or inhibitors of P-glycoprotein or CYP3A4.[21] Oral FXa inhibitors are cleared in part by the kidneys and are metabolized in the liver, which limits their utility in patients with severe kidney or liver disease. In addition, since patients with brain cancer, hematological malignancies, or severe thrombocytopenia were excluded or underrepresented in the trials comparing the oral FXa inhibitors with dalteparin for the treatment of CAT, adjusted-dose LMWH is often the preferred option in these patients.

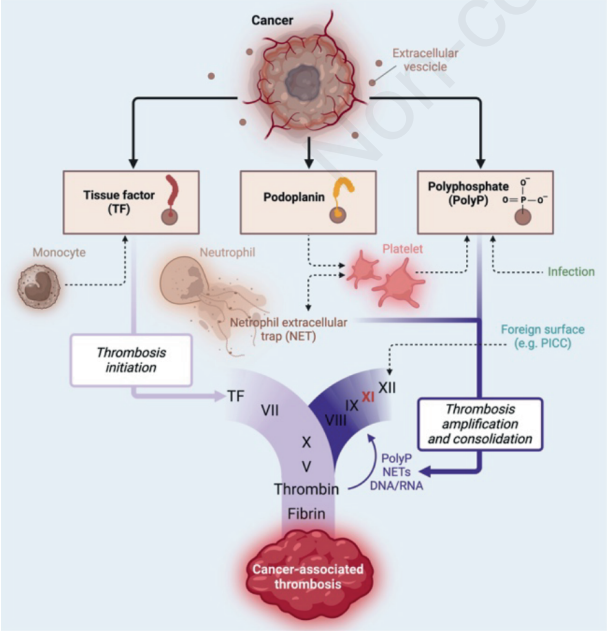

Figure 1. Role of factor XI in the pathophysiology of cancer-associated thrombosis.

Limitations of current cancer-associated thrombosis treatments

Bleeding remains the major concern with both oral FXa inhibitors and LMWH.[20] The risk of bleeding with current anticoagulants is related to their inhibitory effects on both thrombosis and hemostasis because they target FXa and thrombin, which are implicated in the common coagulation pathway.[23] Preclinical and clinical evidence suggests that thrombosis can be uncoupled from hemostasis by targeting FXI, which is situated upstream to FXa in the intrinsic pathway of coagulation and is essential for thrombosis, but mostly dispensable for hemostasis.[23] Therefore, anticoagulants that target FXI have the potential to be safer than the currently available agents.

Role of factor XI in cancer-associated thrombosis

FXI can be activated by FXIIa or by thrombin. Regardless of the activator, FXIa is likely to play a central role in the pathophysiology of CAT (Figure 1).[24] The extrinsic coagulation pathway is initiated by tissue factor (TF) exposed at the site of blood vessel injury, or expressed on leukocytes or microvesicles that become tethered to activated endothelial cells. This pathway is particularly important in patients with cancer because some cancer cell types constitutively express TF and release extracellular vesicles bearing TF.[25,26] In addition, increased expression of TF by monocytes has been reported in cancer patients.[1] TF binds FVII or FVIIa to form the TF-FVIIa complex, which activates FX and FIX. FIXa together with FVIIIa assemble on the surface of activated platelets to form intrinsic tenase, which amplifies and sustains FXa and thrombin generation. Since the capability of the TF-FVIIa complex to propagate coagulation may be limited once the thrombus extends beyond the TF source, feedback activation of FXI by thrombin is thought to be essential for thrombus growth.[23]

Activation of FXI by FXIIa may also contribute to CAT. FXII activation can be triggered by negatively charged polyanions including neutrophil extracellular traps released by activated neutrophils, DNA or RNA released from cancer cells, or by polyphosphate released from activated platelets or from bacteria during infections.[27-31] Central venous catheters (CVCs) are often used in patients with cancer for the administration of chemotherapy or other medications, or for blood product transfusion. Contact of the blood with CVCs triggers FXII activation (Figure 1).[32] The relevance of FXII and FXI to catheter thrombosis is highlighted by studies in rabbits that revealed attenuation of catheter-related thrombosis with reduction in the levels of FXII or FXI with target-specific antisense oligonucleotides (ASOs).[33]

Preclinical and epidemiological evidence supporting factor XI as a safer target than factor Xa

Mice deficient in FXI or FXII exhibited defective thrombus formation at sites of arterial or venous injury without evidence of increased bleeding.[34-41] Likewise, antibodies against FXI inhibited thrombosis in rodent models without affecting bleeding, and a reduction in the level of FXI with ASOs reduced shunt thrombosis in baboons.[41] Studies comparing the effects of antibodies against factor FXI or FXII in non-human primates suggested more potent antithrombotic effects with FXI-directed antibodies.[24,42-44]

Epidemiological data support the relevance of FXI in thrombosis. Elevated FXI levels were associated with increased VTE risk,[45-47] and congenital deficiency protected against VTE and ischemic stroke with little or no bleeding.[48-52] The evidence that FXI deficiency is protective against myocardial infarction is less consistent.[48,49] In Mendelian randomization studies, lower FXI levels were associated with reduced risks of VTE and ischemic stroke without an increased risk of major bleeding,[47] whereas high FXI levels were associated with a higher risk of VTE and ischemic stroke.[52,53] These findings align with the observations that subjects with congenital FXI deficiency rarely have spontaneous bleeding and do not experience the muscle, joint, or intracranial bleeding that often occurs in persons with hemophilia A or B.[54,55] Although spontaneous bleeding is rare in patients with congenital FXI deficiency, bleeding can occur after trauma or surgery, often at anatomic regions with increased fibrinolytic activity such as the gastrointestinal and genitourinary tract, and the nasopharynx.[48-50,54-56]

In contrast to FXI, the epidemiological evidence linking FXII with thrombosis is weaker. Despite robust data showing that FXII deficiency or inhibition attenuates arterial and venous thrombosis in animal models, epidemiologic studies failed to demonstrate protection from thrombosis in patients with FXII deficiency and reported an inconsistent association between higher FXII levels and thrombotic risk.[46,57,58] FXII inhibition may also potentially be of limited benefit in settings such as cancer where TF is the major driver of thrombin generation because feedback activation of FXI by thrombin can bypass FXII inhibition.[37,59] Because of the uncertain role of FXII in thrombosis, FXI has gained attention as the more attractive target.[52]

Pharmacological strategies targeting factor XI

As shown in Table 1, multiple pharmacologic strategies to inhibit FXI are under clinical development. These include: i) ASOs (*e.g.*, fesomersen) that reduce the hepatic synthesis of FXI; ii) monoclonal antibodies (*e.g.*, gruticibart, osocimab, abelacimab) that inhibit FXI activation, FXIa activity, or both; iii) small molecules (*e.g.*, asundexian, milvexian) that block the active site of FXIa (Figure 2). Each strategy has its strengths and weaknesses. ASOs and monoclonal antibodies require parenteral administration, while small molecules are given orally. ASOs have a slow onset of action requiring 3-4 weeks of subcutaneous administration to lower FXI levels within therapeutic ranges, which limits their usefulness for the initial treatment of thrombosis or immediate thromboprophylaxis.[52] Although second-generation ligand-conjugated ASOs like fesomersen have a more rapid onset of action of 1-2 weeks, this is still too slow to enable their use for acute VTE treatment. Small molecules have a rapid onset of action as do monoclonal antibodies if they are given intravenously, achieving maximum plasma concentrations 2-4 hours after administration, and thus enabling their use for acute

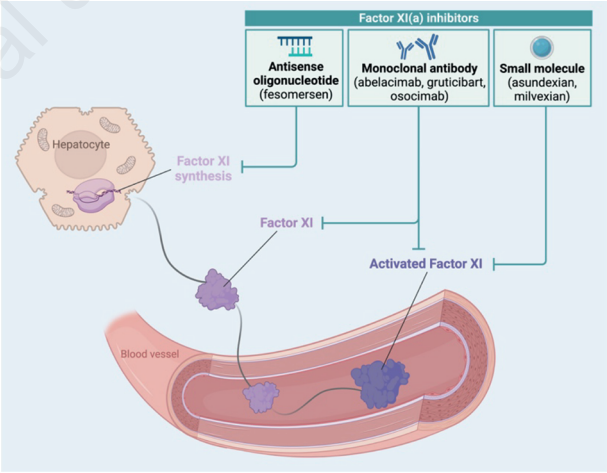

Figure 2. Pharmacologic strategies to inhibit factor XI.

Table 1. Pharmacological features of factor XI-directed strategies.

	Antisense oligonucleotides (fesomersen)	Monoclonal antibodies (abelacimab, gruticibart, osocimab)	Small molecules (asundexian, milvexian)
Mechanism of action	Block synthesis	Bind target protein	Bind target protein
Administration route	Subcutaneous	Intravenous or subcutaneous	Oral
Administration frequency	Weekly to monthly	Monthly	Daily
Onset of action	Slow (weeks)	Rapid (hours to days)	Rapid (1 to 4 hours)
Offset of action	Slow (weeks)	Slow (weeks)	Rapid (12 to 24 hours)
Renal clearance	No	No	Yes
CYP450 metabolism	No	No	Yes*
Potential for drug-drug interactions	No	No	Yes*

*Asundexian is not metabolized via the CYP system. CYP, cytochrome.

management. Small molecules have a short half-life and require once- or twice-daily administration, whereas ASOs and monoclonal antibodies have a long half-life allowing once-monthly subcutaneous dosing. While more convenient, the long half-life of ASOs and monoclonal antibodies could be problematic in case of serious bleeding or trauma, or in patients requiring urgent surgery. Small molecules are partly cleared by the kidneys, and milvexian is metabolized to a small extent by CYP3A4, thus there is a potential for accumulation of asundexian and milvexian in patients with kidney failure and for drug-drug interactions with milvexian.[60-62]

Clinical studies with factor XI inhibitors

The clinical evaluation of new anticoagulants usually starts in patients undergoing major orthopedic surgery because such patients are at risk for postoperative DVT that can be efficiently detected by venography. Although DVT is often asymptomatic in such patients, its presence or absence can help to inform dose selection. Following this drug development pathway, fesomersen, osocimab, abelacimab, and milvexian were compared with enoxaparin for VTE thromboprophylaxis after elective knee replacement surgery.[63-66] A meta-analysis of these studies showed a 40-50% reduction in post-operative VTE and a 59% reduction in clinically relevant bleeding with FXI inhibitors compared with enoxaparin.[67]

The safety of long-term FXI inhibition with abelacimab was highlighted by the results of the phase II AZALEA study that compared monthly subcutaneous abelacimab in doses of 90 mg or 150 mg with rivaroxaban (20 mg once daily) in 1282 patients with atrial fibrillation and a median CHA_2DS_2-VASc score of 5 (https://www.acc.org/Latest-in-Cardiology/Clinical-Trials/2023/11/10/22/46/azalea-timi-71). Abelacimab at the 150 mg dose was associated with a 67% reduction in major and clinically relevant non-major bleeding, a 74% reduction in major bleeding, and a 93% reduction in major gastrointestinal bleeding compared with rivaroxaban. The incidence of stroke and systemic embolism was low (~1%) and comparable between the two groups. Although the results of the AZALEA study have yet to be published, these preliminary data support the safety of long-term potent FXI inhibition with 150 mg of abelacimab compared with rivaroxaban.

Abelacimab is the only FXI inhibitor that has advanced to phase III evaluation in CAT. Abelacimab is currently under investigation in two multicenter, randomized, open-label phase III studies for the treatment of CAT (Table 2). In the ASTER trial (NCT05171049), 1655 patients with cancer and acute VTE, including symptomatic or incidental lower limb acute DVT and/or symptomatic or incidental PE involving a segmental or more proximal pulmonary artery will be randomized to abelacimab or apixaban for 6 months. The MAGNOLIA trial (NCT05171075) will include approximately 1020 patients with unresectable, locally advanced, metastatic, or non-metastatic gastrointestinal or genitourinary cancer and acute VTE. Since edoxaban and rivaroxaban were associated with more bleeding than with dalteparin in patients with these types of cancer and guidelines give preference to LMWH,[15-18] abelacimab is compared with dalteparin in the MAGNOLIA study. In both phase III trials, abelacimab is given at a dose of 150 mg once monthly with the first dose administered intravenously to ensure rapid FXI inhibition and subsequent doses given subcutaneously. Abelacimab has potential limitations including the lack of a specific antidote. However, strategies to prevent or treat bleeding include the administration of tranexamic acid, low-dose FVIIa, or activated prothrombin complex concentrates.[68] Concern has also been raised about the possibility that the high level of TF expression by some tumors may result in such explosive thrombin generation that feedback activation of FXI by thrombin could be potentially bypassed.[37,59] Although this phenomenon has been observed in some animal models, the fact that patient recruitment in the ASTER and MAGNOLIA trials is continuing suggests that this is unlikely to be a major issue in humans.

Gruticibart, an antibody that binds FXI and blocks its activation by FXIIa, was evaluated for the prevention of catheter-related thrombosis in a small, non-randomized phase II trial.[69] In this study, 22 ambulatory cancer patients undergoing central line placement received a single dose (2 mg/kg, through the catheter within 24 of placement) of gruticibart, and underwent ultrasound evaluation on day 14. Compared with no intervention, gruticibart reduced the incidence of catheter-related thrombosis on surveillance ultrasound from 40% to 12.5% (Table 2).[69]

Conclusions and future directions

Robust preclinical and clinical data in patients with atrial fibrillation and patients undergoing orthopedic surgery support FXI inhibition as a potential paradigm shift in the prevention and treatment of CAT. Abelacimab, a monoclonal antibody tar-

Table 2. Completed and ongoing studies of factor XI inhibitors in patients with cancer.

Drug	Mechanism	Route	Study (NCT number)	Indication	N	Comparator
Abelacimab	Monoclonal antibody against FXI and FXIa	Intravenous followed by subcutaneous	ASTER NCT05171049	CAT	1655	Apixaban
		Intravenous followed by subcutaneous	MAGNOLIA NCT05171075	CAT, GI/GU	1020	Dalteparin
Gruticibart	Monoclonal antibody that blocks FXI activation	Intravenous	NCT04465760	Prophylaxis for CVC-related thrombosis in cancer	22	None (single arm)

CAT, cancer-associated thrombosis; CVC, central venous catheter; GI, gastrointestinal; GU, genitourinary; IV, intravenous; SC, subcutaneous.

geting both FXI and FXIa, holds promise for reducing bleeding risk compared with current anticoagulants and overcoming some of the limitations of the oral FXa inhibitors by eliminating the potential for drug-drug interactions and concerns about kidney or hepatic dysfunction. The reduction in gastrointestinal bleeding with abelacimab compared with rivaroxaban observed in the AZALEA trial suggests that eliminating active drugs in the gut may reduce local bleeding, which could provide abelacimab with an advantage over oral FXa inhibitors for CAT treatment in patients with gastrointestinal cancers.

With its long half-life, abelacimab may be an ideal agent for primary prophylaxis in high-risk cancer patients receiving chemotherapy or for postoperative thromboprophylaxis after major cancer surgery. FXI inhibitors may also have a role in the prevention of catheter-related thrombosis, as suggested by a small phase 2 study with gruticibart.[69] The results of the ASTER and MAGNOLIA trials, whose completion is expected in 2025, will establish the safety and efficacy of abelacimab in this highly challenging clinical scenario and may prompt investigation into the utility of the oral FXIa for the prevention and treatment of CAT.

References

1. Khorana AA, Mackman N, Falanga A, et al. Cancer-associated venous thromboembolism. Nat Rev Dis Primers 2022; 8:11.
2. Mulder FI, Horváth-Puhó E, van Es N, et al. Venous thromboembolism in cancer patients: a population-based cohort study. Blood 2021;137:1959-69.
3. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. J Thromb Haemost 2007;5: 632-4.
4. Lloyd AJ, Dewilde S, Noble S, et al. What impact does venous thromboembolism and bleeding have on cancer patients' quality of life? Value Health 2018;21:449-55.
5. Sharp L, Carsin AE, Timmons A. Associations between cancer-related financial stress and strain and psychological well-being among individuals living with cancer. Psychooncology 2013;22:745-55.
6. Cohen AT, Katholing A, Rietbrock S, et al. Epidemiology of first and recurrent venous thromboembolism in patients with active cancer. A population-based cohort study. Thromb Haemost 2017;117:57-65.
7. Prandoni P, Lensing AW, Piccioli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002;100:3484-8.
8. Noble S, Prout H, Nelson A. Patients' Experiences of LIving with CANcer-associated thrombosis: the PELICAN study. Patient Prefer Adherence 2015;9:337-45.
9. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018;378:615-24.
10. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol 2018;36:2017-23.
11. Planquette B, Bertoletti L, Charles-Nelson A, et al. Rivaroxaban vs dalteparin in cancer-associated thromboembolism: a randomized trial. Chest 2022;161:781-90.
12. McBane RD 2nd, Wysokinski WE, Le-Rademacher JG, et al. Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial. J Thromb Haemost 2020;18:411-21.
13. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020;382:1599-607.
14. Schrag D, Uno H, Rosovsky R, et al. Direct oral anticoagulants vs low-molecular-weight heparin and recurrent vte in patients with cancer: a randomized clinical trial. JAMA 2023;329:1924-33.
15. Lyman GH, Carrier M, Ay C, et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv 2021;5:927-74.
16. 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;38:496-520.
17. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. Ann Oncol 2023;34:452-67.
18. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. J Clin Oncol 2023;41:3063-71.
19. Kraaijpoel N, Di Nisio M, Mulder FI, et al. Clinical impact of bleeding in cancer-associated venous thromboembolism: results from the Hokusai VTE cancer study. Thromb Haemost 2018;118:1439-49.
20. Moik F, Posch F, Zielinski C, et al. Direct oral anticoagulants compared to low-molecular-weight heparin for the treatment of cancer-associated thrombosis: updated systematic review and meta-analysis of randomized controlled trials. Res Pract Thromb Haemost 2020;4:550-61.
21. Steffel J, Collins R, Antz M, et al. 2021 European heart rhythm association practical guide on the use of non-vitamin k antagonist oral anticoagulants in patients with atrial fibrillation. Europace 2021;23:1612-76.
22. Wang TF. Drug-drug interactions: Implications for anticoagulation, with focus in patients with cancer. Thromb Res 2022;213:S66-s71.
23. Hsu C, Hutt E, Bloomfield DM, et al Factor XI inhibition to uncouple thrombosis from hemostasis: jacc review topic of the week. J Am Coll Cardiol 2021;78:625-31.
24. Cheng Q, Tucker EI, Pine MS, et al. A role for factor XIIa-mediated factor XI activation in thrombus formation in vivo. Blood 2010;116:3981-9.
25. Geddings JE, Hisada Y, Boulaftali Y, et al. Tissue factor-positive tumor microvesicles activate platelets and enhance thrombosis in mice. J Thromb Haemost 2016;14:153-66.
26. Davila M, Amirkhosravi A, Coll E, et al. Tissue factor-bearing microparticles derived from tumor cells: impact on coagulation activation. J Thromb Haemost 2008;6:1517-24.
27. Shim YJ, Chatterjee V, Swaidani S, et al. Polyphosphate expression by cancer cell extracellular vesicles mediates binding of factor XII and contact activation. Blood Adv 2021;5:4741-51.

28. Nickel KF, Ronquist G, Langer F, et al. The polyphosphate-factor XII pathway drives coagulation in prostate cancer-associated thrombosis. Blood 2015;126:1379-89.
29. Swystun LL, Mukherjee S, Liaw PC. Breast cancer chemotherapy induces the release of cell-free DNA, a novel procoagulant stimulus. J Thromb Haemost 2011;9:2313-21.
30. Fredenburgh JC, Gross PL, Weitz JI. Emerging anticoagulant strategies. Blood 2017;129:147-54.
31. Long AT, Kenne E, Jung R, et al. Contact system revisited: an interface between inflammation, coagulation, and innate immunity. J Thromb Haemost 2016;14:427-37.
32. Marin A, Bull L, Kinzie M, Andresen M. Central catheter-associated deep vein thrombosis in cancer: clinical course, prophylaxis, treatment. BMJ Support Palliat Care 2021;11: 371-80.
33. Yau JW, Liao P, Fredenburgh JC, et al. Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. Blood 2014;123: 2102-7.
34. Wang X, Cheng Q, Xu L, et al. Effects of factor IX or factor XI deficiency on ferric chloride-induced carotid artery occlusion in mice. J Thromb Haemost 2005;3:695-702.
35. Wang X, Smith PL, Hsu MY, et al. Effects of factor XI deficiency on ferric chloride-induced vena cava thrombosis in mice. J Thromb Haemost 2006;4:1982-8.
36. Ay C, Hisada Y, Cooley BC, Mackman N. Factor XI-deficient mice exhibit increased bleeding after injury to the saphenous vein. J Thromb Haemost 2017;15:1829-33.
37. Schumacher WA, Seiler SE, Steinbacher TE, et al. Antithrombotic and hemostatic effects of a small molecule factor XIa inhibitor in rats. Eur J Pharmacol 2007;570: 167-74.
38. Revenko AS, Gao D, Crosby JR, et al. Selective depletion of plasma prekallikrein or coagulation factor XII inhibits thrombosis in mice without increased risk of bleeding. Blood 2011;118:5302-11.
39. Renné T, Pozgajová M, Grüner S, et al. Defective thrombus formation in mice lacking coagulation factor XII. J Exp Med 2005;202:271-81.
40. Renné T, Oschatz C, Seifert S, et al. Factor XI deficiency in animal models. J Thromb Haemost 2009;7:79-83.
41. Grover SP, Mackman N. Intrinsic pathway of coagulation and thrombosis. Arterioscler Thromb Vasc Biol 2019;39: 331-8.
42. Younis HS, Crosby J, Huh JI, et al. Antisense inhibition of coagulation factor XI prolongs APTT without increased bleeding risk in cynomolgus monkeys. Blood 2012;119: 2401-8.
43. Matafonov A, Leung PY, Gailani AE, et al. Factor XII inhibition reduces thrombus formation in a primate thrombosis model. Blood 2014;123:1739-46.
44. Gruber A, Hanson SR. Factor XI-dependence of surface- and tissue factor-initiated thrombus propagation in primates. Blood 2003;102:953-5.
45. Meijers JC, Tekelenburg WL, Bouma BN, et al. High levels of coagulation factor XI as a risk factor for venous thrombosis. N Engl J Med 2000;342:696-701.
46. Cushman M, O'Meara ES, Folsom AR, Heckbert SR. Coagulation factors IX through XIII and the risk of future venous thrombosis: the longitudinal investigation of thromboembolism etiology. Blood 2009;114:2878-83.
47. Georgi B, Mielke J, Chaffin M, et al. Leveraging human genetics to estimate clinical risk reductions achievable by inhibiting factor XI. Stroke 2019;50:3004-12.
48. Preis M, Hirsch J, Kotler A, et al. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. Blood 2017;129:1210-5.
49. Salomon O, Steinberg DM, Koren-Morag N, et al. Reduced incidence of ischemic stroke in patients with severe factor XI deficiency. Blood 2008;111:4113-7.
50. Salomon O, Steinberg DM, Zucker M, et al. Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis. Thromb Haemost 2011;105:269-73.
51. Stavrou E, Schmaier AH. Factor XII: what does it contribute to our understanding of the physiology and pathophysiology of hemostasis & thrombosis. Thromb Res 2010;125:210-5.
52. Weitz JI. Factor XI and factor XII as targets for new anticoagulants. Thromb Res 2016;141:S40-5.
53. Yuan S, Burgess S, Laffan M, et al. Genetically proxied inhibition of coagulation factors and risk of cardiovascular disease: a mendelian randomization study. J Am Heart Assoc 2021;10:e019644.
54. Key NS. Epidemiologic and clinical data linking factors XI and XII to thrombosis. Hematol Am Soc Hematol Educ Program 2014;2014:66-70.
55. Asakai R, Chung DW, Davie EW, Seligsohn U. Factor XI deficiency in Ashkenazi Jews in Israel. N Engl J Med 1991;325:153-8.
56. Weitz JI, Chan NC. Advances in antithrombotic therapy. Arterioscler Thromb Vasc Biol 2019;39:7-12.
57. Johnson CY, Tuite A, Morange PE, et al. The factor XII -4C>T variant and risk of common thrombotic disorders: A HuGE review and meta-analysis of evidence from observational studies. Am J Epidemiol 2011;173:136-44.
58. Doggen CJ, Rosendaal FR, Meijers JC. Levels of intrinsic coagulation factors and the risk of myocardial infarction among men: Opposite and synergistic effects of factors XI and XII. Blood 2006;108:4045-51.
59. Mäder J, Rolling CC, Voigtländer M, et al. Effect of factor XI inhibition on tumor cell-induced coagulation activation. J Thromb Haemost 2023;22:199-212.
60. Dilger AK, Pabbisetty KB, Corte JR, et al. Discovery of milvexian, a high-affinity, orally bioavailable inhibitor of factor XIa in clinical studies for antithrombotic therapy. J Med Chem 2022;65:1770-85.
61. Wong PC, Crain EJ, Bozarth JM, et al. Milvexian, an orally bioavailable, small-molecule, reversible, direct inhibitor of factor XIa: In vitro studies and in vivo evaluation in experimental thrombosis in rabbits. J Thromb Haemost 2022;20: 399-408.
62. Kubitza D, Heckmann M, Distler J, et al. Pharmacokinetics, pharmacodynamics and safety of BAY 2433334, a novel activated factor XI inhibitor, in healthy volunteers: a randomized phase 1 multiple-dose study. Br J Clin Pharmacol 2022;88:3447-62.
63. Büller HR, Bethune C, Bhanot S, et al. Factor XI antisense oligonucleotide for prevention of venous thrombosis. N Engl J Med 2015;372:232-40.
64. Weitz JI, Bauersachs R, Becker B, et al. Effect of osocimab in preventing venous thromboembolism among patients un-

dergoing knee arthroplasty: the FOXTROT randomized clinical trial. JAMA 2020;323:130-9.
65. Weitz JI, Strony J, Ageno W, et al. Milvexian for the prevention of venous thromboembolism. N Engl J Med 2021;385:2161-72.
66. Verhamme P, Yi BA, Segers A, et al. Abelacimab for prevention of venous thromboembolism. N Engl J Med 2021; 385:609-17.
67. Nopp S, Kraemmer D, Ay C. Factor XI inhibitors for prevention and treatment of venous thromboembolism: a review on the rationale and update on current evidence. Front Cardiovasc Med 2022;9:903029.
68. van Es N, De Caterina R, Weitz JI. Reversal agents for current and forthcoming direct oral anticoagulants. Eur Heart J 2023;44:1795-806.
69. Pfeffer MA, Kohs TCL, Vu HH, et al. Factor XI inhibition for the prevention of catheter-associated thrombosis in patients with cancer undergoing central line placement: a phase 2 clinical trial. Arterioscler Thromb Vasc Biol 2024; 44:290-9.