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Factor XI as a Target for New Anticoagulants

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Abstract—The goal of anticoagulant therapy is to attenuate thrombosis without compromising hemostasis. Although the direct oral anticoagulants are associated with less intracranial hemorrhage than vitamin K antagonists, bleeding remains their major side effect. Factor XI has emerged as a promising target for anticoagulants that may be safer than those currently available. The focus on factor XI stems from epidemiological evidence of its role in thrombosis, the observation of attenuated thrombosis in factor XI-deficient mice, identification of novel activators, and the fact that factor XI deficiency is associated with only a mild bleeding diathesis. Proof-of-concept comes from the demonstration that compared with enoxaparin, factor XI knockdown reduces venous thromboembolism without increasing bleeding after elective knee arthroplasty. This article rationalizes the selection of factor XI as a target for new anticoagulants, reviews the agents under development, and outlines a potential path forward for their development.

Visual Overview—An online [visual overview](#) is available for this article. (*Arterioscler Thromb Vasc Biol.* 2018;38:304-310. DOI: 10.1161/ATVBAHA.117.309664.)

Key Words: anticoagulant ■ factor XI ■ hemostasis ■ thrombin ■ thrombosis

We are on the verge of a new era of anticoagulation therapy with the development of factor XI inhibitors. The anticoagulant journey started early in the 20th century with the introduction of heparin and vitamin K antagonists (VKAs), the first agents to establish the role of anticoagulants in curbing thrombosis (Figure 1).¹ The next era of anticoagulation therapy focused on refining the formulation of heparin with the development of low-molecular-weight heparin and fondaparinux.² With better bioavailability after subcutaneous injection than heparin and more predictable anticoagulant responses, low-molecular-weight heparin and fondaparinux enabled out-of-hospital treatment without the need for coagulation monitoring, thereby reducing healthcare costs and increasing patient satisfaction. Coincident with these advances was the development of bivalirudin, a thrombin-specific parenteral inhibitor derived from the leech protein hirudin, which is widely used in place of heparin during percutaneous coronary interventions and for treatment of heparin-induced thrombocytopenia.³ The success of bivalirudin, which inhibits thrombin, and fondaparinux, which inhibits factor Xa, provided evidence that targeting these downstream clotting enzymes was both effective and safe.

See Insight Into Jeffrey I. Weitz on page 311

Advances in oral anticoagulation beyond the VKAs were slow to come. Driven by a quest for oral anticoagulants that were more convenient to administer than VKAs and enabled by advances in

the structural characterization of thrombin and factor Xa, this generation of drugs includes dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, edoxaban, and betrixaban, which inhibit factor (F) Xa.⁴ Known as direct oral anticoagulants (DOACs), these agents are at least as effective as VKAs but are associated with less bleeding, particularly less intracranial bleeding, and are easier to administer because they can be given in fixed doses without routine coagulation monitoring. Because of these attributes, current guidelines give preference to the DOACs over VKAs for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism in patients without active cancer.^{5,6} Prescriptions for DOACs now surpass those for VKAs in several countries and are likely to increase as new indications are identified.^{7,8}

Although there is less bleeding with the DOACs than with VKAs, bleeding remains their major side effect. Even with the DOACs, fear of bleeding is at least one driver of the systemic underuse of anticoagulants in atrial fibrillation patients at high risk of stroke revealed in contemporary registries.^{9,10} These findings have prompted the search for anticoagulants that are safer than the DOACs. Recent epidemiological and animal studies have suggested that FXI, a coagulation factor upstream to thrombin and FXa, is a potential target to achieve this goal.¹¹ This review outlines the rationale for targeting upstream coagulation factors, identifies FXI as the ideal candidate, summarizes current progress, and highlights what is in the pipeline for the next era of anticoagulants.

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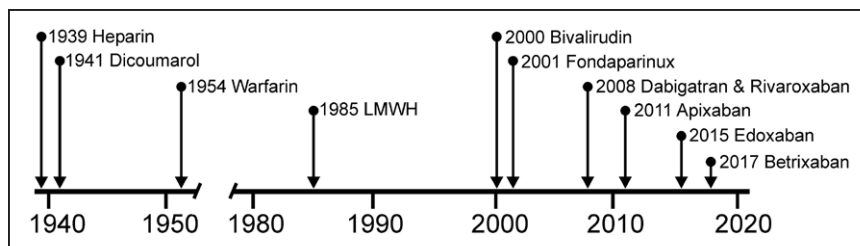


Figure 1. Timeline for the development of anticoagulants. LMWH indicates low-molecular weight heparin.

Role of FXI in Coagulation

Before the DOACs, anticoagulants mainly targeted thrombin and FXa, and their minor effects on upstream enzymes such as FXII or FXI were deemed secondary. However, modeling and experimental studies suggest that anticoagulants that target these upstream clotting factors may be effective because of the amplifying nature of sequential activation steps in the coagulation cascade.¹² Exposed at sites of vascular injury, tissue factor (TF) binds FVIIa, and this complex then triggers the generation of thrombin via activation of FX, comprising the extrinsic pathway. Subsequently, the intrinsic pathway augments FX activation and thrombin generation through the formation of intrinsic tenase (Figure 2). Engagement of the intrinsic pathway is mediated by FIX activation by the TF–FVIIa complex and by FXI activation by thrombin. The intrinsic pathway is responsible for the bulk of FXa generation because intrinsic tenase, composed of FIXa and FVIIIa assembled on a membrane surface, is a more efficient activator of FX than TF/FVIIa,¹³ and because once bound to FXa, tissue factor pathway inhibitor effectively inactivates FVIIa in complex with TF.¹⁴ Therefore, the intrinsic pathway is essential for efficient thrombin generation.

FIX is activated by FXIa, which results from cleavage of FXI by FXIIa or thrombin. FXIa is generated via the contact pathway by the reciprocal activation of FXII and prekallikrein, which autoactivate and transactivate in the presence of negatively charged surfaces. The source of such surfaces is thought to be anionic polymers released from activated cells and platelets, including DNA, RNA, and inorganic polyphosphate.¹⁵ Two decades ago, thrombin-mediated activation of FXI was the postulated explanation for the absence of a bleeding diathesis in patients with congenital FXII deficiency.¹⁶ More recently, it has been observed that the same polyanions that promote the contact pathway also stimulate back activation of FXI by thrombin, thereby identifying nucleic acids and polyphosphates as important cofactors in thrombosis.^{15,17,18} Therefore, identification of pathological mechanisms for activation of FXII and FXI supports their attention as potential targets for new anticoagulants.

Why Target FXI?

Interest in FXI as a target for anticoagulants stems from basic and epidemiological studies that suggest that the contact factors are important in thrombosis.^{19–21} Support for a more prominent role of FXI over FXII in thrombosis comes from epidemiological studies (Table 1). Notably, congenital FXI deficiency is protective against venous thromboembolism (VTE), ischemic stroke, and myocardial infarction, whereas FXII deficiency not only is not protective but also may increase the risk.²² Furthermore, subjects with higher levels of FXI are more prone to ischemic

stroke and VTE, whereas those with elevated FXII levels are not, and FXI levels correlate with stroke risk in women taking oral contraceptives.^{22–24} Finally, patients with hereditary angioedema as a consequence of impaired regulation of FXIIa and kallikrein are not prone to thrombosis. Therefore, epidemiological studies support the role of FXI in thrombosis, but not FXII.

Animal studies also suggest that FXI is more important than FXII in thrombosis. In a baboon arteriovenous shunt model, antibodies against FXI attenuated platelet and fibrin deposition more than those directed against FXII.^{25,26} In the same model, FXI knockdown with an antisense oligonucleotide (ASO) reduced thrombosis in a concentration-dependent manner once FXI levels were <50% of normal.²⁷

Results in rodent models are different; in these models, FXI and FXII seem to be equally important drivers of thrombosis. Thus, in arterial or venous injury models, mice deficient in FXII

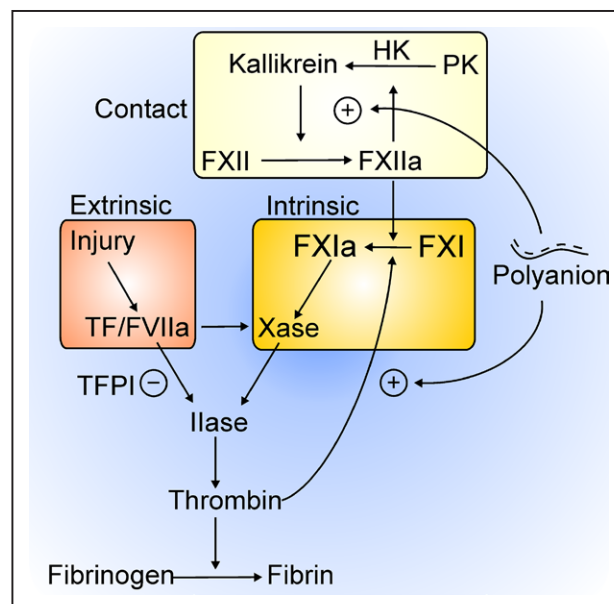


Figure 2. Overview of coagulation system. Coagulation is initiated by the extrinsic pathway when tissue factor (TF) exposed at sites of vascular injury binds and activates factor (F) VII. The activated FVII (FVIIa)–TF complex activates FX in the common pathway to generate prothrombinase (IIase), which generates thrombin. This pathway is downregulated by tissue factor pathway inhibitor (TFPI), which inhibits FVIIa in a FXa-dependent manner. Alternative activation of coagulation occurs when the contact system, consisting of FXII, prekallikrein (PK), and high-molecular weight kininogen (HK), is exposed to polyanions released from activated platelets and neutrophils. Generated FXIIa then activates FXI, which promotes formation of intrinsic tenase (Xase) and subsequently prothrombinase. Because polyanions promote activation of FXI by thrombin, this feedback mechanism provides an ancillary pathway of thrombin formation after the initiating stimulus by TF/FVIIa is pacified by inhibitors. HK indicates ; and PK, .

Table 1. Relative Advantages and Disadvantages of Factor XII or Factor XI as Targets for New Anticoagulants

	Factor XII	Factor XI
Epidemiological data	Weak	Stronger
Risk of bleeding	None	Low
Level of evidence for role in thrombosis	Preclinical	Phase 2
Potential for bypassing inhibition	Thrombin-mediated activation of factor XI could bypass factor XII inhibition	TF/factor VIIa-mediated activation of factor IX could bypass factor XI inhibition
Potential for off-target effects	May modulate inflammation by inhibiting bradykinin generation	Unlikely

TF indicates tissue factor.

are equally or more protected from thrombosis than those deficient in FXI.^{25,28,29} Likewise, FXII-deficient mice are protected from ischemic stroke and form smaller thrombi after venous flow restriction.³⁰ Therefore, there may be species-dependent differences in the contribution of FXI and FXII to thrombosis.

The importance of the contact system in thrombosis may vary depending on the trigger for initiation of coagulation. For example, FXII may be an important driver of clotting on blood-contacting medical devices or extracorporeal circuits because thrombosis on artificial surfaces is initiated by FXII activation.³¹ Thus, catheters coated with corn trypsin inhibitor, which inhibits FXIIa, remain patent longer than control catheters when inserted in the jugular veins of rabbits.³² Likewise, in the same rabbit model, FXII knockdown prolongs the catheter-induced occlusion time by >2-fold,³³ and a FXIIa-directed antibody is as effective as heparin at preventing clotting in an extracorporeal membrane oxygenation circuit in rabbits but produces less bleeding.³⁴ Therefore, these studies suggest that contact activation of FXII initiates clotting on artificial surfaces.

Although the data predominantly favor FXI, FXII remains a viable target. One advantage of FXII is safety. Strategies targeting FXII will not induce bleeding because FXII has no role in hemostasis. In contrast, strategies targeting FXI may be associated with bleeding, particularly mucosal bleeding, which occurs in patients with severe FXI deficiency.³⁵ However, targeting FXII may be of limited benefit when thrombosis is initiated by TF because thrombin generated via extrinsic tenase has the potential to activate FXI, thereby bypassing FXII inhibition.¹⁶ Furthermore, although FXII depletion reduced thrombin generation induced by components of mechanical heart valves to background levels, FXI depletion abolished it.³⁶ Therefore, despite some evidence for a role for FXII in thrombosis, epidemiological and primate studies point to a more robust association between FXI levels and the risk of thrombosis.^{37–43} As with established anticoagulant strategies, the choice between targeting FXI and FXII will likely be predicated on balancing efficacy with the risk of bleeding. Consequently because of the epidemiological and animal model data outlined above, FXI is emerging as the preferred target for new anticoagulants.

Strategies to Inhibit FXI

Strategies to inhibit FXI are illustrated in Table 2 and include (1) ASOs that reduce hepatic synthesis of the clotting protein^{27,33,44}; (2) monoclonal antibodies that block FXI activation, FXIa activity, or both^{25,45,46}; (3) aptamers that block FXI activation or activity^{47,48}; and (4) small molecules that block the active site of FXIa^{49–51} or induce allosteric modulation.^{52,53} Each strategy not only differs in terms of mechanism of action but has unique pharmacological characteristics that impact therapeutic approaches (Table 3). Thus, ASOs, antibodies, and aptamers require parenteral administration, whereas active site inhibitors have the potential for parenteral or oral delivery. The pharmacological onset and offset of action of these agents also varies. Up to a month of ASO treatment is required to lower FXI levels into the therapeutic range, which limits their use for initial treatment of thrombosis or for immediate thromboprophylaxis.^{27,33,44} In contrast, small-molecule inhibitors and antibodies typically achieve therapeutic levels within minutes or hours of administration. The prolonged half-life of FXI-directed antibodies or ASOs could be problematic if there is bleeding with trauma or surgery. Plasma or FXI concentrate will replace FXI in patients treated with ASOs, but a bypassing agent such as recombinant FVIIa would be needed to overcome the effect of inhibitory antibodies. Conversely, like the DOACs, small molecules benefit from rapid clearance, with half-lives <24 hours. With such short half-lives, antidotes are unlikely to be required. Therefore, each strategy has strengths and weaknesses.

Clinical Data

The first FXI-specific strategy to be tested in humans was the FXI-directed ASO IONIS-416858, which is given subcutaneously. After a 4-week regimen, the ASO reduced FXI antigen and activity levels in a concentration-dependent manner in healthy volunteers.⁵⁴ The ASO was then tested in a phase 2 study that enrolled 300 patients undergoing elective knee arthroplasty. Patients were randomized to receive 200 or 300 mg of subcutaneous IONIS-416858 starting 35 days before surgery or 40-mg enoxaparin once daily starting after surgery and continued for at least 10 days.⁵⁵ At the time of surgery, mean FXI levels were reduced to 38% and 28% of baseline values in the groups receiving the 200- and 300-mg IONIS-416858 doses, respectively. The primary efficacy outcome was VTE, which included the composite of asymptomatic or symptomatic deep-vein thrombosis, symptomatic pulmonary

Table 2. Strategies to Target Factor XI

Strategy	Mechanism of Action
Antisense oligonucleotides	Reduce hepatic synthesis of factor XI
Aptamers	Bind factor XI and block activity
Antibodies	Bind factor XI and block activation or activity
Small molecules	Bind reversibly to active site of factor XIa and block its activity
Polyanion antagonists	Neutralize polyphosphates or nucleic acids via ionic interactions, thereby attenuating contact pathway activation

Table 3. Pharmacological Features of Factor XI–Directed Strategies

Feature	Antisense Oligonucleotides	Antibodies	Aptamers	Small Molecules
Delivery	Parenteral	Parenteral	Parenteral	Parenteral or oral
Specific	Yes	Yes	Yes	Yes
Onset of action	Delayed	Immediate	Immediate	Immediate
Offset of action	Delayed	Delayed	Rapid	Rapid
Renal clearance	No	No	No	Variable
Hepatic metabolism	No	No	No	Variable
Potential clinical indications	Chronic	Acute or chronic	Acute or chronic	Acute or chronic

embolism, and VTE-related mortality, whereas the principal safety outcome was a composite of major and clinically relevant nonmajor bleeding. The primary efficacy outcome occurred in 36 of 134 patients (27%) who received the 200-mg dose of IONIS-416858 and in 3 of 71 patients (4%) who received the 300-mg dose of IONIS-416858, as compared with 21 of 69 patients (30%) receiving enoxaparin. The 200-mg IONIS-416858 regimen was noninferior, whereas the 300-mg regimen was superior to enoxaparin ($P < 0.001$). The rates of the composite of major and clinically relevant nonmajor bleeding were 3% in both IONIS-416858 groups and 8% in the enoxaparin groups. Although the results of this small phase 2 study suggest that lowering FXI levels reduces the risk of postoperative VTE to a greater extent than enoxaparin without increasing the risk of bleeding, confirmatory data from larger trials are needed.

Because thrombin generation after major orthopedic surgery likely results from TF exposure at the surgical site, these findings challenge our thinking about the pathogenesis of postoperative venous thrombosis. There are 2 potential explanations for the reduced risk of VTE with targeting of FXI. First, TF-induced thrombin generation may amplify coagulation by feedback activation of FXI. Second, surgery may trigger the release of DNA and RNA from damaged cells and polyphosphate from activated platelets that directly activate FXII. Knockdown of FXI prevents propagation of coagulation by both pathways (Figure 2). With this proof-of-principle in hand, we now can start to identify additional clinical indications for FXI-directed strategies.

Potential Indications for FXI-Directed Therapies

More studies are needed to confirm the efficacy of FXI-directed strategies for VTE prevention and to identify other indications (Table 4). Until it is known whether inhibition of FXI is sufficient for treatment of established venous or arterial thrombosis when used as sole therapy, it may be better to focus on prevention. Because of their slow onset of action, FXI-directed ASOs are best suited for chronic indications, such as secondary prevention in patients with unprovoked VTE, prevention of cardiovascular events in patients with chronic kidney disease, stroke prevention in atrial fibrillation patients at high risk for bleeding, such as those with end-stage renal disease who are on hemodialysis, and secondary prevention in patients with cerebrovascular, coronary, or peripheral

artery disease. Prevention in patients with unprovoked VTE is a potential indication because the risk of recurrent thrombosis is $\approx 10\%$ at 1 year and 30% at 5 years if anticoagulant therapy is stopped.⁵⁶ Being on indefinite anticoagulant therapy carries a risk of bleeding, even with the DOACs.⁵⁷ Therefore, FXI-directed strategies with once-monthly injections of ASOs or antibodies may be safer and be associated with better adherence than oral medications that must be taken once or twice daily.

Another potential indication for FXI-directed therapy is stroke prevention in hemodialysis patients with atrial fibrillation because the DOACs have not been tested in this setting and because there is uncertainty as to whether the benefits of warfarin outweigh the harms.^{58,59} Inhibition of FXI may also attenuate clotting on the hemodialysis circuit, thereby further lowering the risk of bleeding associated with heparin therapy. In support of this concept, a small pilot study in hemodialysis patients revealed less clotting in the air trap and on the dialysis membrane with IONIS-416858 at doses of 200 or 300 mg than with placebo even though all patients received heparin during dialysis.⁶⁰ The reduction in FXI levels with IONIS-416858 in hemodialysis patients was similar to that in patients undergoing knee replacement surgery, thereby setting the stage for its use in patients with end-stage disease. This is a relevant target population because even without atrial fibrillation, patients on hemodialysis are at risk of cardiovascular events and such events are responsible for at least 50% of the mortality.⁶¹ Therefore, FXI-directed strategies may provide an effective and safe method for reducing major adverse cardiovascular events in these high-risk patients.

Targeting FXI for prevention of clotting on extracorporeal membrane oxygenation circuits may be safer than heparin and safer than warfarin for prevention of thromboembolic events in patients with left ventricular assist devices. Because targeting thrombin with dabigatran failed versus warfarin in patients with mechanical heart valves,⁶² FXI-directed strategies may provide an effective alternative because FXI depletion abolishes mechanical valve-induced thrombin generation *in vitro*.³⁶

FXI-directed strategies may be safer than currently available anticoagulants in patients requiring concomitant antiplatelet therapy (Table 4). Thus, when added to dual antiplatelet therapy in patients with acute coronary syndrome, low-dose rivaroxaban reduced the risk of recurrent ischemic events and stent thrombosis but at a cost of increased bleeding,

Table 4. Potential Indications for Factor XI–Directed Strategies

Indication	Rationale
Primary VTE prophylaxis	Long-acting strategies such as antisense oligonucleotides or antibodies permit simple and safe single-dose regimens for extended thromboprophylaxis in medically ill patients or after major orthopedic surgery
Secondary VTE prophylaxis	May be safer than current therapies for secondary prevention in patients with unprovoked or cancer-associated venous thromboembolism
Prevention of recurrent ischemia after acute coronary syndrome	May provide a safer anticoagulant platform on top of single or dual antiplatelet therapy
Secondary prevention of major adverse cardiovascular events in patients with cerebrovascular, coronary, or peripheral artery disease	May be safer than currently available anticoagulants as an adjunct to aspirin
Prevention of recurrent stroke or major adverse cardiovascular events in patients with noncardioembolic ischemic stroke	May be more effective than aspirin alone for prevention of recurrent ischemia
End-stage renal disease	May be safe and effective for reducing cardiovascular death, myocardial infarction, and stroke in patients on hemodialysis
High-risk atrial fibrillation patients	May be safer than current therapies for stroke prevention in atrial fibrillation patients at high risk for bleeding such as those with a history of major bleeding or with end-stage renal disease
Medical devices	May be more effective and safer than current therapies to prevent clotting on mechanical heart valves, left ventricular assist devices, small caliber grafts or central venous catheters
Extracorporeal circuits	May be more effective and safer than heparin to prevent clotting on extracorporeal membrane oxygenator or cardiopulmonary bypass circuits

VTE indicates venous thromboembolism.

including intracranial bleeding.⁶³ Likewise, when added to aspirin for secondary prevention in patients with stable coronary or peripheral artery disease, low-dose rivaroxaban reduced the risk of cardiovascular death, stroke, or myocardial infarction compared with aspirin alone but increased the risk of bleeding.⁶⁴ FXI-directed strategies would likely be safer than rivaroxaban and should block contact activation on stents and prevent FXI-mediated thrombus stabilization and growth at sites of atherosclerotic plaque disruption.

The efficacy and safety of targeting FXI may vary significantly depending on the specific clinical situation. Results with the FXI-directed ASO have already shown that orthopedic surgery is a potentially viable indication. However,

FXI-deficient individuals are more prone to bleeding in the nasopharyngeal and reproductive tracts than in other sites, suggesting that tissues with high fibrinolytic activity may be more dependent on FXI than others.¹¹ Furthermore, FXI levels are poorly correlated with the risk of bleeding.⁶⁵ Despite these limitations, however, FXI remains an attractive target for novel anticoagulant strategies. Accordingly, additional phase 2 studies with FXI-directed strategies are expected in the near future. These studies will confirm the role of FXI in thrombosis, provide additional safety information, and help identify potential phase 3 indications.

Conclusions and Future Directions

Recent advances have catalyzed examination of targets beyond those involved in the terminal reactions of the coagulation pathway. With evidence that the contact system is important for thrombus stabilization and growth, FXI and FXII have emerged as promising targets for new anticoagulants that are likely to be safer than those that inhibit FXa or thrombin. ASOs, aptamers, antibodies, and small molecules provide a growing armamentarium of agents to determine whether FXI or FXII is the better target and to compare the efficacy and safety of these new strategies with current standards of care for prevention or treatment of thrombosis. Selection of indications should focus on unmet medical needs, particularly those where current therapies have limited efficacy or safety. The clinical potential of FXII- and FXI-directed anticoagulant strategies should be clarified over the next few years.

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Disclosures

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References

- Mannucci PM, Franchini M. Old and new anticoagulant drugs: a minireview. *Ann Med*. 2011;43:116–123. doi: 10.3109/07853890.2010.539250.
- Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e24S–e43S. doi: 10.1378/chest.11–2291.
- Shah R, Rogers KC, Matin K, Askari R, Rao SV. An updated comprehensive meta-analysis of bivalirudin vs heparin use in primary percutaneous coronary intervention. *Am Heart J*. 2016;171:14–24. doi: 10.1016/j.ahj.2015.10.006.
- Chan NC, Eikelboom JW, Weitz JI. Evolving treatments for arterial and venous thrombosis: role of the direct oral anticoagulants. *Circ Res*. 2016;118:1409–1424. doi: 10.1161/CIRCRESAHA.116.306925.
- Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC). Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Endorsed by the European Stroke Organisation (ESO). *Eur Heart J*. 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210.
- Kearon C, Akl EA, Ornella J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE,

- Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149:315–352. doi: 10.1016/j.chest.2015.11.026.
7. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med*. 2015;128:1300–1305.e2. doi: 10.1016/j.amjmed.2015.05.044.
 8. Weitz JI, Semchuk W, Turpie AG, Fisher WD, Kong C, Ciaccia A, Cairns JA. Trends in prescribing oral anticoagulants in Canada, 2008–2014. *Clin Ther*. 2015;37:2506–2514. doi: 10.1016/j.clinthera.2015.09.008.
 9. Huisman MV, Rothman KJ, Paquette M, Teutsch C, Diener HC, Dubner SJ, Halperin JL, Ma C, Zint K, Elsaesser A, Bartels DB, Lip GY; GLORIA-AF Investigators. Antithrombotic treatment patterns in patients with newly diagnosed nonvalvular atrial fibrillation: The GLORIA-AF Registry, Phase II. *Am J Med*. 2015;128:1306–1313.e1. doi: 10.1016/j.amjmed.2015.07.013.
 10. Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk: insights from the NCDR PINNACLE registry. *JAMA Cardiol*. 2016;1:55–62. doi: 10.1001/jamacardio.2015.0374.
 11. Gailani D, Gruber A. Factor XI as a therapeutic target. *Arterioscler Thromb Vasc Biol*. 2016;36:1316–1322. doi: 10.1161/ATVBAHA.116.306925.
 12. Mann KG, Butenas S, Brummel K. The dynamics of thrombin formation. *Arterioscler Thromb Vasc Biol*. 2003;23:17–25.
 13. Hockin MF, Jones KC, Everse SJ, Mann KG. A model for the stoichiometric regulation of blood coagulation. *J Biol Chem*. 2002;277:18322–18333. doi: 10.1074/jbc.M201173200.
 14. Mast AE. Tissue factor pathway inhibitor: multiple anticoagulant activities for a single protein. *Arterioscler Thromb Vasc Biol*. 2016;36:9–14. doi: 10.1161/ATVBAHA.115.305996.
 15. Naudin C, Burillo E, Blankenberg S, Butler L, Renné T. Factor XII contact activation. *Semin Thromb Hemost*. 2017;43:814–826. doi: 10.1055/s-0036-1598003.
 16. Gailani D, Broze GJ Jr. Factor XI activation in a revised model of blood coagulation. *Science*. 1991;253:909–912.
 17. Gajisiewicz JM, Smith SA, Morrissey JH. Polyphosphate and RNA differentially modulate the contact pathway of blood clotting. *J Biol Chem*. 2017;292:1808–1814. doi: 10.1074/jbc.M116.754325.
 18. Preissner KT, Herwald H. Extracellular nucleic acids in immunity and cardiovascular responses: between alert and disease. *Thromb Haemost*. 2017;117:1272–1282. doi: 10.1160/TH-16-11-0858.
 19. Weitz JI. Factor XI and factor XII as targets for new anticoagulants. *Thromb Res*. 2016;141(suppl 2):S40–S45. doi: 10.1016/S0049-3848(16)30363-2.
 20. Gailani D. Future prospects for contact factors as therapeutic targets. *Hematology Am Soc Hematol Educ Program*. 2014;2014:52–59. doi: 10.1182/asheducation-2014.1.52.
 21. van Montfoort ML, Meijers JC. Recent insights into the role of the contact pathway in thrombo-inflammatory disorders. *Hematology Am Soc Hematol Educ Program*. 2014;2014:60–65. doi: 10.1182/asheducation-2014.1.60.
 22. Key NS. Epidemiologic and clinical data linking factors XI and XII to thrombosis. *Hematology Am Soc Hematol Educ Program*. 2014;2014:66–70. doi: 10.1182/asheducation-2014.1.66.
 23. Gailani D, Bane CE, Gruber A. Factor XI and contact activation as targets for antithrombotic therapy. *J Thromb Haemost*. 2015;13:1383–1395. doi: 10.1111/jth.13005.
 24. Preis M, Hirsch J, Kotler A, Zoabi A, Stein N, Rennert G, Saliba W. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood*. 2017;129:1210–1215. doi: 10.1182/blood-2016-09-742262.
 25. Cheng Q, Tucker EI, Pine MS, Sisler I, Matafonov A, Sun MF, White-Adams TC, Smith SA, Hanson SR, McCarty OJ, Renné T, Gruber A, Gailani D. A role for factor XIIa-mediated factor XI activation in thrombus formation in vivo. *Blood*. 2010;116:3981–3989. doi: 10.1182/blood-2010-02-270918.
 26. Matafonov A, Leung PY, Gailani AE, Grach SL, Puy C, Cheng Q, Sun MF, McCarty OJ, Tucker EI, Kataoka H, Renné T, Morrissey JH, Gruber A, Gailani D. Factor XII inhibition reduces thrombus formation in a primate thrombosis model. *Blood*. 2014;123:1739–1746. doi: 10.1182/blood-2013-04-499111.
 27. Zhang H, Löwenberg EC, Crosby JR, MacLeod AR, Zhao C, Gao D, Black C, Revenko AS, Meijers JC, Stroes ES, Levi M, Monia BP. Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. *Blood*. 2010;116:4684–4692. doi: 10.1182/blood-2010-04-277798.
 28. Renné T, Pozgajová M, Grüner S, Schuh K, Pauer HU, Burfeind P, Gailani D, Nieswandt B. Defective thrombus formation in mice lacking coagulation factor XII. *J Exp Med*. 2005;202:271–281. doi: 10.1084/jem.20050664.
 29. Renné T, Oschatz C, Seifert S, Müller F, Antovic J, Karlman M, Benz PM. Factor XI deficiency in animal models. *J Thromb Haemost*. 2009;7(suppl 1):79–83. doi: 10.1111/j.1538-7836.2009.03393.x.
 30. Revenko AS, Gao D, Crosby JR, Bhattacharjee G, Zhao C, May C, Gailani D, Monia BP, MacLeod AR. Selective depletion of plasma prekallikrein or coagulation factor XII inhibits thrombosis in mice without increased risk of bleeding. *Blood*. 2011;118:5302–5311. doi: 10.1182/blood-2011-05-355248.
 31. Jaffer IH, Fredenburgh JC, Hirsh J, Weitz JI. Medical device-induced thrombosis: what causes it and how can we prevent it? *J Thromb Haemost*. 2015;13(suppl 1):S72–S81. doi: 10.1111/jth.12961.
 32. Yau JW, Stafford AR, Liao P, Fredenburgh JC, Roberts R, Brash JL, Weitz JI. Corn trypsin inhibitor coating attenuates the prothrombotic properties of catheters in vitro and in vivo. *Acta Biomater*. 2012;8:4092–4100. doi: 10.1016/j.actbio.2012.07.019.
 33. Yau JW, Liao P, Fredenburgh JC, Stafford AR, Revenko AS, Monia BP, Weitz JI. Selective depletion of factor XI or factor XII with antisense oligonucleotides attenuates catheter thrombosis in rabbits. *Blood*. 2014;123:2102–2107. doi: 10.1182/blood-2013-12-540872.
 34. Larsson M, Rayzman V, Nolte MW, et al. A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci Transl Med*. 2014;6:222ra17. doi: 10.1126/scitranslmed.3006804.
 35. Seligsohn U. Factor XI deficiency in humans. *J Thromb Haemost*. 2009;7(suppl 1):84–87. doi: 10.1111/j.1538-7836.2009.03395.x.
 36. Jaffer IH, Stafford AR, Fredenburgh JC, Whitlock RP, Chan NC, Weitz JI. Dabigatran is less effective than warfarin at attenuating mechanical heart valve-induced thrombin generation. *J Am Heart Assoc*. 2015;4:e002322. doi: 10.1161/JAHA.115.002322.
 37. Meijers JC, Tekelenburg WL, Bouma BN, Bertina RM, Rosendaal FR. High levels of coagulation factor XI as a risk factor for venous thrombosis. *N Engl J Med*. 2000;342:696–701. doi: 10.1056/NEJM200003093421004.
 38. 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;114:2878–2883. doi: 10.1182/blood-2009-05-219915.
 39. Siegerink B, Govers-Riemsag JW, Rosendaal FR, Ten Cate H, Algra A. Intrinsic coagulation activation and the risk of arterial thrombosis in young women: results from the Risk of Arterial Thrombosis in relation to Oral contraceptives (RATIO) case-control study. *Circulation*. 2010;122:1854–1861. doi: 10.1161/CIRCULATIONAHA.110.943738.
 40. 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;108:4045–4051. doi: 10.1182/blood-2005-12-023697.
 41. Salomon O, Steinberg DM, Dardik R, Rosenberg N, Zivelin A, Tamarin I, Ravid B, Berliner S, Seligsohn U. Inherited factor XI deficiency confers no protection against acute myocardial infarction. *J Thromb Haemost*. 2003;1:658–661.
 42. Koster T, Rosendaal FR, Briët E, Vandenbroucke JP. John Hageman's factor and deep-vein thrombosis: Leiden thrombophilia Study. *Br J Haematol*. 1994;87:422–424.
 43. Zeerleder S, Schloesser M, Redondo M, Wuillemin WA, Engel W, Furlan M, Lämmle B. Reevaluation of the incidence of thromboembolic complications in congenital factor XII deficiency—a study on 73 subjects from 14 Swiss families. *Thromb Haemost*. 1999;82:1240–1246.
 44. Crosby JR, Marzec U, Revenko AS, Zhao C, Gao D, Matafonov A, Gailani D, MacLeod AR, Tucker EI, Gruber A, Hanson SR, Monia BP. Antithrombotic effect of antisense factor XI oligonucleotide treatment in primates. *Arterioscler Thromb Vasc Biol*. 2013;33:1670–1678. doi: 10.1161/ATVBAHA.113.301282.
 45. David T, Kim YC, Ely LK, Rondon I, Gao H, O'Brien P, Bolt MW, Coyle AJ, Garcia JL, Flounders EA, Mikita T, Coughlin SR. Factor XIa-specific IgG and a reversal agent to probe factor XI function in thrombosis and hemostasis. *Sci Transl Med*. 2016;8:353ra112. doi: 10.1126/scitranslmed.aaf4331.
 46. Tucker EI, Marzec UM, White TC, Hurst S, Rugonyi S, McCarty OJ, Gailani D, Gruber A, Hanson SR. Prevention of vascular graft occlusion and thrombus-associated thrombin generation by inhibition of factor XI. *Blood*. 2009;113:936–944. doi: 10.1182/blood-2008-06-163675.

47. Donkor DA, Bhakta V, Eltringham-Smith LJ, Stafford AR, Weitz JI, Sheffield WP. Selection and characterization of a DNA aptamer inhibiting coagulation factor XIa. *Sci Rep*. 2017;7:2102. doi: 10.1038/s41598-017-02055-x.
48. Woodruff RS, Ivanov I, Verhamme IM, Sun MF, Gailani D, Sullenger BA. Generation and characterization of aptamers targeting factor XIa. *Thromb Res*. 2017;156:134–141. doi: 10.1016/j.thromres.2017.06.015.
49. Deng H, Bannister TD, Jin L, et al. Synthesis, SAR exploration, and X-ray crystal structures of factor XIa inhibitors containing an alpha-ketothiazole arginine. *Bioorg Med Chem Lett*. 2006;16:3049–3054. doi: 10.1016/j.bmcl.2006.02.052.
50. Wong PC, Crain EJ, Watson CA, Schumacher WA. A small-molecule factor XIa inhibitor produces antithrombotic efficacy with minimal bleeding time prolongation in rabbits. *J Thromb Thrombolysis*. 2011;32:129–137. doi: 10.1007/s11239-011-0599-0.
51. Quan ML, Wong PC, Wang C, et al. Tetrahydroquinoline derivatives as potent and selective factor XIa inhibitors. *J Med Chem*. 2014;57:955–969. doi: 10.1021/jm401670x.
52. Al-Horani RA, Ponnusamy P, Mehta AY, Gailani D, Desai UR. Sulfated pentagalloylglucoside is a potent, allosteric, and selective inhibitor of factor XIa. *J Med Chem*. 2013;56:867–878. doi: 10.1021/jm301338q.
53. Al-Horani RA, Desai UR. Designing allosteric inhibitors of factor XIa. Lessons from the interactions of sulfated pentagalloylglucopyranosides. *J Med Chem*. 2014;57:4805–4818. doi: 10.1021/jm500311e.
54. Liu Q, Bethune C, Dessouki E, Gundy J, Monia BP, Bhanot S. ISIS-FIX-Rx, a novel and specific antisense inhibitor of factor XI, caused a significant reduction in FXI antigen and activity and increased aPTT without causing bleeding in healthy volunteers. *Blood*. 2011;118:Abstract 209.
55. Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med*. 2015;372:232–240. doi: 10.1056/NEJMoa1405760.
56. Kearon C. Natural history of venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I22–I30. doi: 10.1161/01.CIR.0000078464.82671.78.
57. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. *J Thromb Haemost*. 2014;12:320–328. doi: 10.1111/jth.12485.
58. Shen JI, Turakhia MP, Winkelmayr WC. Anticoagulation for atrial fibrillation in patients on dialysis: are the benefits worth the risks? *Curr Opin Nephrol Hypertens*. 2012;21:600–606. doi: 10.1097/MNH.0b013e32835856fd.
59. Nochaiwong S, Ruengorn C, Awiphan R, Dandecha P, Noppakun K, Phrommintikul A. Efficacy and safety of warfarin in dialysis patients with atrial fibrillation: a systematic review and meta-analysis. *Open Heart*. 2016;3:e000441. doi: 10.1136/openhrt-2016-000441.
60. Ionispharma. Pipeline: Clinical. <http://www.ionispharma.com/pipeline/>. 2017; Accessed September 25, 2017.
61. Bhatti NK, Karimi GK, Paz Y et al. Diagnosis and management of cardiovascular disease in advanced and end-stage renal disease. *J Am Heart Assoc*. 2016;5:e003648. doi: 10.1161/JAHA.116.003648.
62. Eikelboom JW, Connolly SJ, Brueckmann M, et al; RE-ALIGN Investigators. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med*. 2013;369:1206–1214. doi: 10.1056/NEJMoa1300615.
63. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;366:9–19. doi: 10.1056/NEJMoa1112277.
64. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118.
65. Bolton-Maggs PH, Young Wan-Yin B, McCraw AH, Slack J, Kernoff PB. Inheritance and bleeding in factor XI deficiency. *Br J Haematol*. 1988;69:521–528.

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