

JACC REVIEW TOPIC OF THE WEEK

Factor XI Inhibition to Uncouple Thrombosis From Hemostasis



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ABSTRACT

Hemostasis and thrombosis are believed to be so intricately linked that any strategies that reduce thrombosis will have an inevitable impact on hemostasis. Consequently, bleeding is viewed as an unavoidable side effect of anticoagulant therapy. Emerging evidence suggests that factor XI is important for thrombosis but has a minor role in hemostasis. This information raises the possibility that anticoagulants that target factor XI will be safer than currently available agents. The authors provide a visual representation of the coagulation pathways that distinguishes between the steps involved in thrombosis and hemostasis to explain why factor XI inhibitors may serve as hemostasis-sparing anticoagulants. A safer class of anticoagulants would provide opportunities for treatment of a wider range of patients, including those at high risk for bleeding. Ongoing clinical studies will determine the extent to which factor XI inhibitors attenuate thrombosis without disruption of hemostasis. (J Am Coll Cardiol 2021;78:625-631) © 2021 by the American College of Cardiology Foundation.

Thromboembolic disorders are estimated to cause 1 in 4 deaths worldwide. As the common underlying mechanism of venous thromboembolism (VTE) and most cases of myocardial infarction and ischemic stroke, thrombosis is a leading cause of morbidity and mortality (1).

Anticoagulation therapy is a cornerstone for the prevention and treatment of thrombosis. For many years, vitamin K antagonists (VKAs) such as warfarin were the only available oral anticoagulants. Although effective, VKAs are burdensome to administer because the dose varies from person to person. This variability reflects drug-drug and drug-food interactions as well as common genetic polymorphisms

that affect the pharmacokinetic and pharmacodynamic properties of VKAs. Consequently, patients taking VKAs need regular coagulation monitoring and dose adjustment to ensure that the international normalized ratio (INR), the measure of the anticoagulant effect of VKAs, remains within the therapeutic range. If the INR is too low, the risk of thrombosis is increased, and if the INR is too high, the risk of bleeding is increased. Although INR monitoring reduces the risk of bleeding with VKAs, the risk of intracranial hemorrhage, the most feared complication of VKA treatment, is up to 10-fold higher in patients taking VKAs than in those not taking an anticoagulant (2,3). This is despite the INR being



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ABBREVIATIONS AND ACRONYMS

aPTT = activated partial thromboplastin time

DOAC = direct oral anticoagulant

INR = international normalized ratio

TF = tissue factor

VKA = vitamin K antagonist

VTE = venous thromboembolism

within the therapeutic range in at least two-thirds of patients with VKA-associated intracranial bleeding (4).

VKAs exert their antithrombotic effects by lowering the functional levels of the vitamin K-dependent clotting proteins, factor (F) II (prothrombin), FVII, FIX, and FX. Reduction in the levels of prothrombin and FX appears to be most important for achieving a therapeutic effect. Consistent with this, parenteral agents that specifically inhibit the activated forms of these proteins, thrombin (eg, argatroban or bivalirudin) or FXa (eg, fondaparinux), have

proven to be effective anticoagulants. Over the past 15 years, oral inhibitors targeting thrombin (ie, dabigatran) or FXa (ie, rivaroxaban, apixaban, and edoxaban) have become available. These drugs are collectively referred to as direct oral anticoagulants (DOACs). A meta-analysis of pivotal trials of patients with nonvalvular atrial fibrillation showed that, compared with warfarin, the high-dose DOAC regimens were associated with a 19% reduction in the risk of stroke/systemic embolism and a 10% reduction in all-cause mortality. This was accompanied by a 50% reduction in intracranial hemorrhage and a 50% reduction in hemorrhagic stroke (5). Post-marketing observational data are consistent with the randomized trial results for all marketed DOACs, revealing a 40% reduction in major bleeding (6-11).

Despite the improved safety profile of the DOACs compared with VKAs, their use is still associated with a significant risk of bleeding. The fear of bleeding likely contributes to undertreatment of certain types of patients who may benefit from anticoagulation. A recent registry-based study revealed that 13% of patients with atrial fibrillation admitted with stroke had been deemed unsuitable for anticoagulation due to a high bleeding risk. Furthermore, an additional 42% of patients with known atrial fibrillation had not been given an anticoagulant despite being eligible for thromboprophylaxis, indicating that fear of bleeding is an obstacle to anticoagulation (12,13).

Prior to the introduction of the DOACs, VTE treatment started with heparin or low-molecular-weight heparin as patients were bridged to a VKA. Randomized trials comparing this approach with treatment with DOACs revealed a similar risk of recurrent VTE, but a 40% reduction in major bleeding with DOACs (14). Consequently, DOACs rapidly replaced VKAs for VTE treatment. Low-molecular-weight heparins such as dalteparin were the standard of care for treatment of cancer-associated VTE because they were shown to be superior to VKAs for prevention of recurrent VTE (15). Randomized trials comparing DOACs with

HIGHLIGHTS

- Although currently available anticoagulants are effective, bleeding is the most frequent side effect.
- Factor XI is important for thrombosis but less so for hemostasis.
- Factor XI inhibitors may serve as hemostasis-sparing anticoagulants with better safety profiles than currently available anticoagulants.

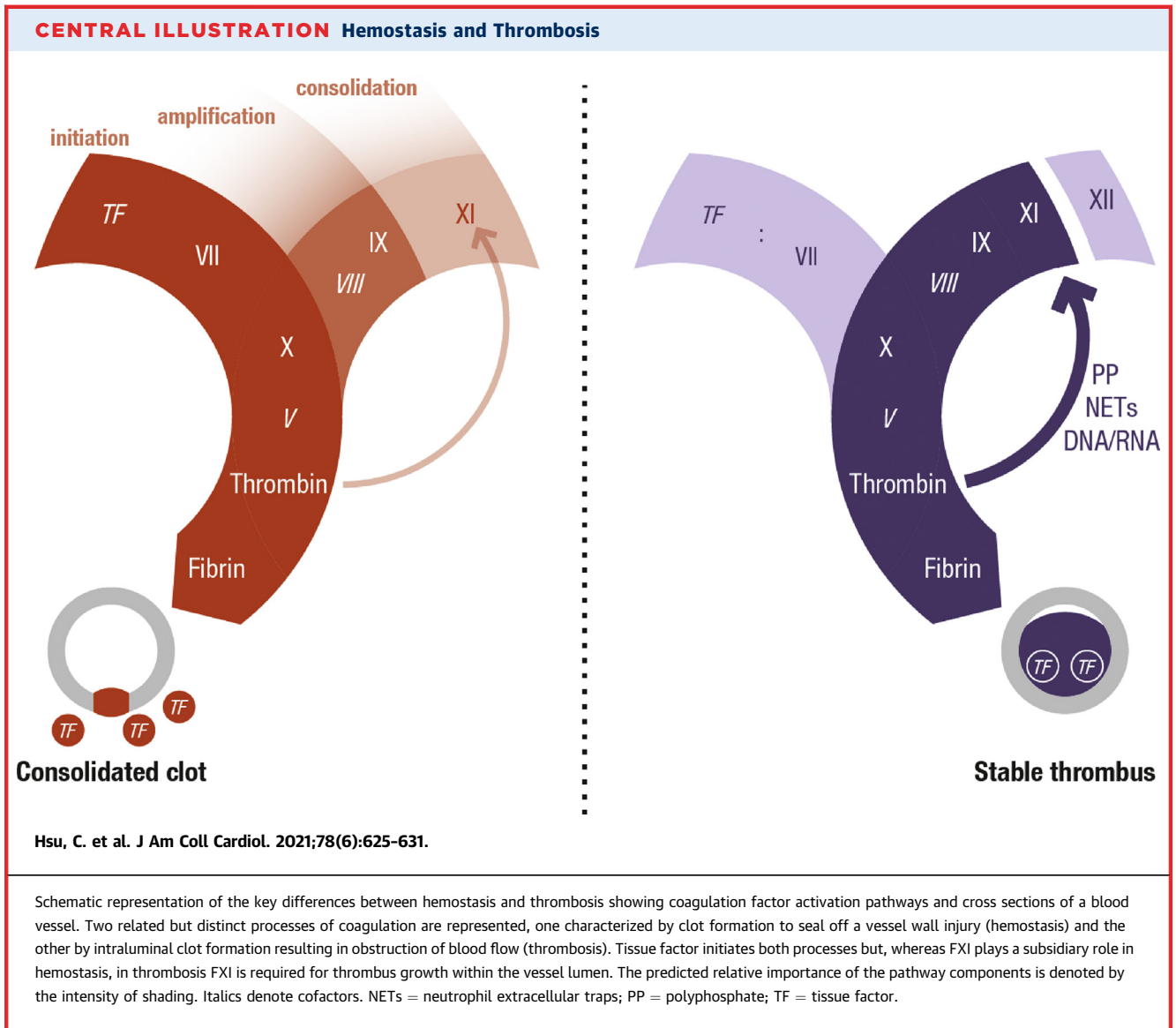
dalteparin in such patients reveal a lower risk of recurrent VTE with the DOACs, but more major bleeding, at least with some of the drugs (16). The excess bleeding with the DOACs in cancer patients mainly reflects gastrointestinal bleeding in those with unresected tumors of the upper gastrointestinal tract. However, even in patients with atrial fibrillation, the rates of gastrointestinal bleeding are higher with some of the DOACs than with warfarin (5). This emphasizes the need for new anticoagulants that spare hemostasis (17).

FXI inhibitors have emerged as a particularly promising class of anticoagulants. With the publication of early- and mid-stage trial data for drugs directed against FXI and its activated form FXIa, it is a good time to take a fresh look at how targeting this protein prevents thrombosis while leaving hemostasis largely intact. In this paper, we propose a new visual framework for coagulation based on the latest science that explains the potential of inhibitors of FXI and FXIa to uncouple thrombosis from hemostasis (**Central Illustration**).

UNCOUPLING HEMOSTASIS AND THROMBOSIS

Hemostasis and thrombosis involve many of the same enzymatic reactions but produce different results, as set out in the **Central Illustration**. In hemostasis, bleeding from injured vessels is stopped by formation of a hemostatic plug within the vessel wall and the immediate extravascular environment. In thrombosis, a thrombus forming within the blood vessel lumen partially or completely blocks blood flow, thereby leading to organ damage (**Central Illustration**). Understanding the similarities and differences in these processes is required for rational design of drugs that uncouple antithrombotic and anti-hemostatic effects.

HEMOSTASIS. The goal of hemostasis, a physiological response to injury to a blood vessel wall, is to seal the leak and to stop bleeding, with minimal

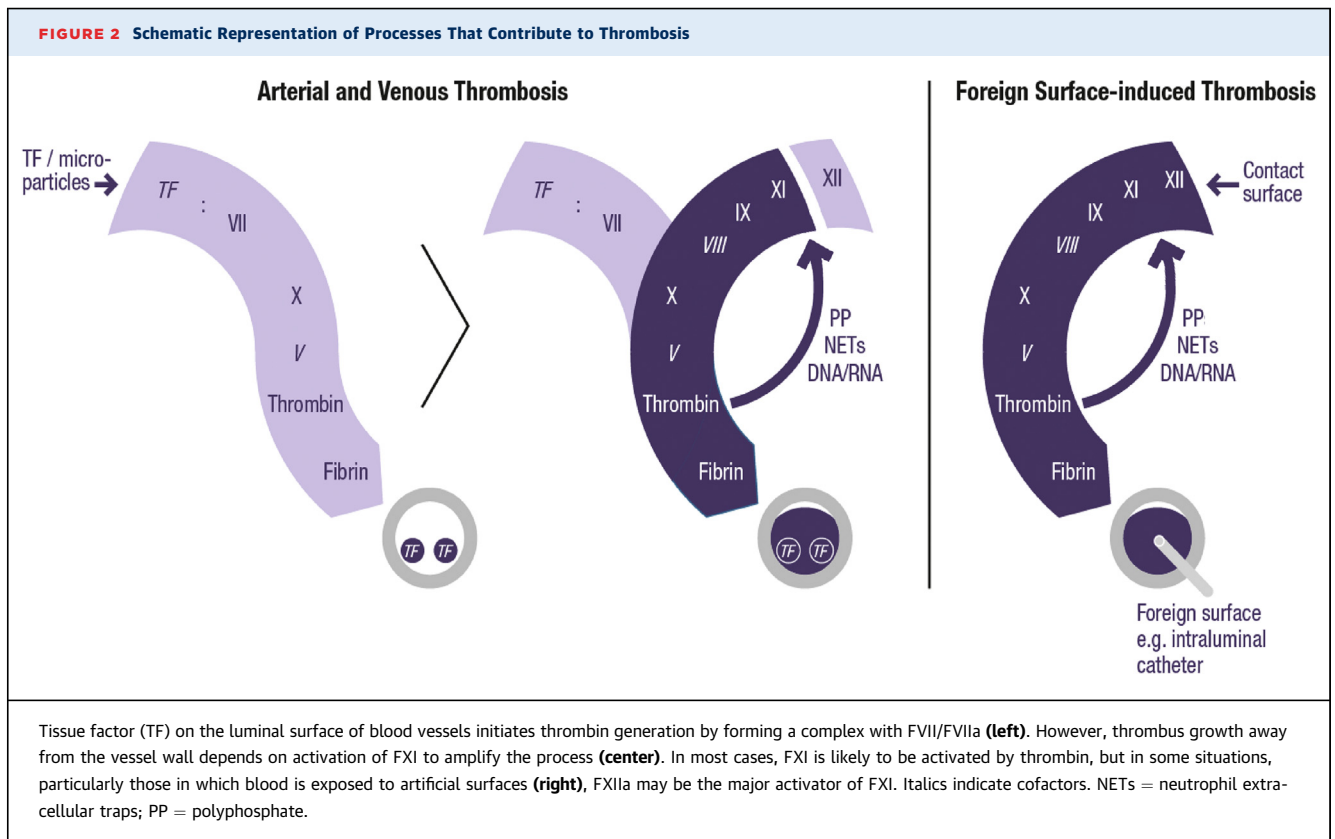
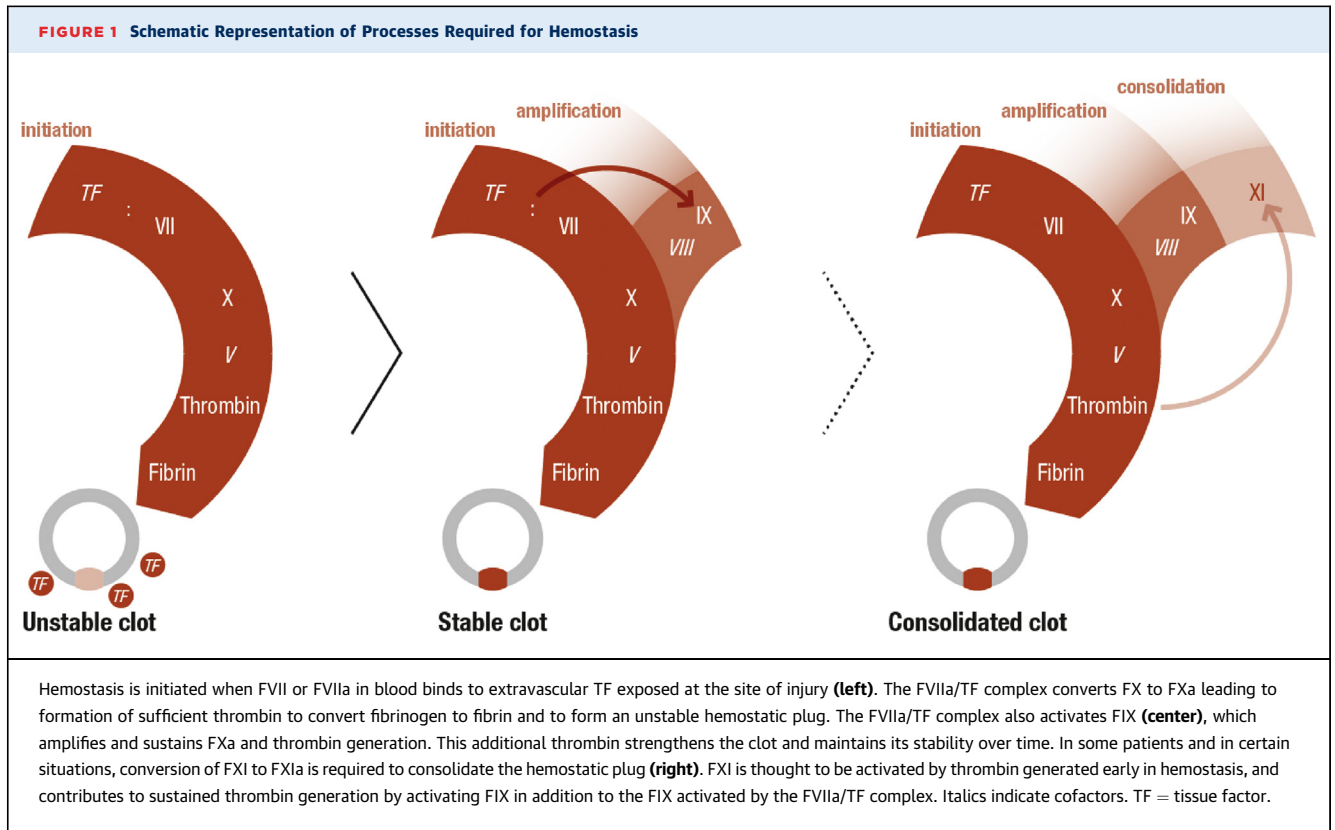


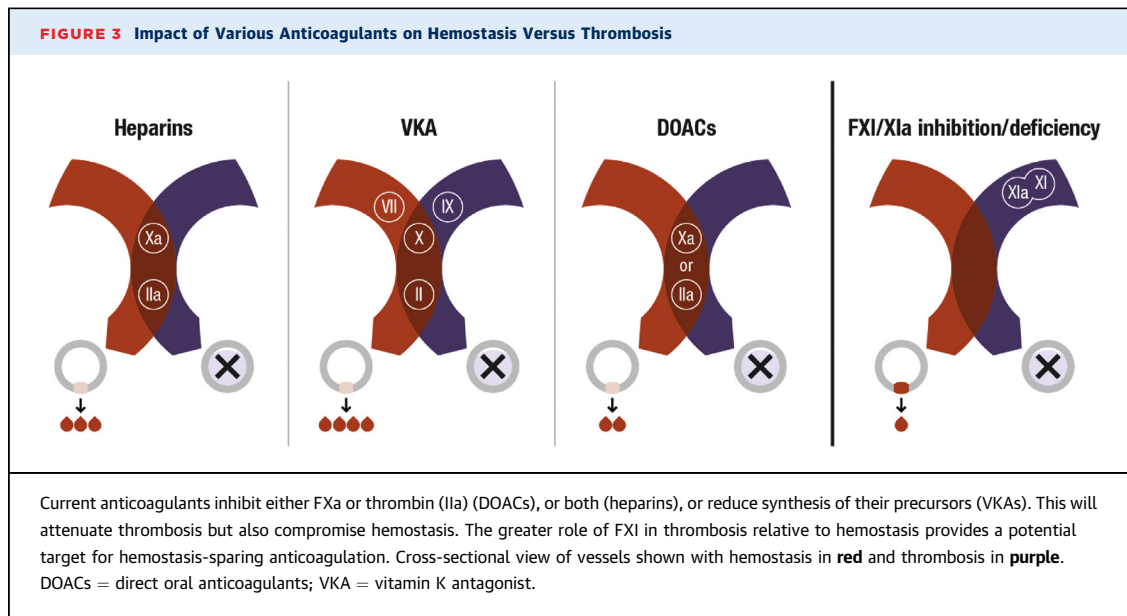
disruption of normal blood flow within vessels. The hemostatic process is initiated when FVII or its activated form FVIIa in blood binds to extravascular tissue factor (TF) exposed at the site of blood vessel injury (Figure 1). The FVIIa:TF complex activates FX to FXa, which then converts a limited amount of prothrombin into the key coagulation enzyme thrombin. This early thrombin generation initiates fibrin formation and, along with FXa, provides positive feedback to activate the key cofactor proteins, FV and FVIII.

The limited amount of thrombin generated early in hemostasis is only sufficient to initiate the response to injury. In addition to activating FX, the FVIIa/TF complex converts FIX to FIXa (Figure 1). FIXa, with its cofactor factor VIIIa, maintains

thrombin generation over hours to days post-injury through sustained activation of FX. The importance of this pathway in hemostasis is reflected by the severe bleeding disorders associated with inherited FVIII or FIX deficiency (hemophilia A and hemophilia B, respectively) (18).

FXI plays a relatively limited role in hemostasis. In some individuals, it is required to stem bleeding with certain types of injuries. During hemostasis, FXI is thought to be converted to FXIa by thrombin, and this process consolidates coagulation through activation of FIX (Figure 1). FXI appears to be most important with injury to the oropharynx and urinary tract. Bleeding in patients with congenital FXI deficiency is relatively mild compared with that in hemophilia A or hemophilia B, and the spontaneous bleeds into





muscles or joints and the life-threatening intracranial or gastrointestinal bleeding seen with hemophilia A or B are not features of FXI deficiency (19).

THROMBOSIS. A pathologic process in which clots form within the blood vessel lumen, thrombosis compromises blood flow. In most cases, thrombus formation appears to be triggered by TF exposed on disrupted vascular endothelium (eg, disrupted atherosclerotic plaques) or expressed on leukocytes, microvesicles, or diseased endothelial cells (Figure 2). However, the capacity of the FVIIa/TF complex to propagate intraluminal thrombus growth may be limited once the thrombus enlarges and extends beyond the TF source at the site of vessel wall damage. Here, FXI may drive thrombus growth (Figure 2). Epidemiological data and studies in animals support the importance of FXI in thrombosis. FXI-deficient individuals have reduced incidences of VTE and ischemic stroke compared with the general population, whereas those with high FXI levels carry more than twice the risk of VTE (20,21). Thrombosis in response to injury is attenuated in mice deficient in FXI, and FXI knockdown or inhibition reduces thrombosis in a variety of animal models (22-25).

Thrombin is likely the predominant activator of FXI in thrombosis. FXIIa appears to be less important because epidemiologic studies fail to show an association between FXII levels and the risk of VTE, ischemic stroke, or myocardial infarction. Nonetheless, naturally occurring polyanions that are likely to be present in a growing thrombus, including chromatin extruded from activated neutrophils

(neutrophil extracellular traps) or inorganic phosphate polymers (polyphosphate) released from activated platelets, can activate FXII and support FXI activation by FXIIa. Furthermore, in situations where thrombosis is triggered by exposure of blood to artificial surfaces (eg, cardiopulmonary bypass, hemodialysis, central venous catheters), thrombin generation may be primarily initiated by FXIIa activation of FXI (Figure 2), rather than by the FVIIa/TF complex. Regardless of the mechanism of FXI activation, on balance, FXIa appears to be more important for thrombosis than for hemostasis.

Therapies directed at FXI or FXIa have demonstrated efficacy in preventing VTE in patients undergoing total knee arthroplasty in two phase 2 studies (26,27). During knee arthroplasty, a number of factors may increase VTE risk including exposure of blood to TF, collagen, or products of cell breakdown such as nucleic acids and polyphosphate. FXI reduction achieved by administering an antisense oligonucleotide starting 35 days before surgery, or FXIa inhibition with osocimab, an inhibitory antibody given immediately before or after surgery, was at least as effective as standard therapy in preventing postoperative VTE in patients undergoing total knee arthroplasty. Importantly, therapy directed at FXI/FXIa did not appear to compromise hemostasis. Thus, many of the patients who received the antisense oligonucleotide or osocimab preoperatively had the full effect of FXI inhibition therapy during surgery and did not have excessive bleeding (26,27). An ideal treatment would have the same efficacy and bleeding profile as the antisense oligonucleotide but would have a rapid

onset of action, which would enable administration after surgery.

The models for hemostasis and thrombosis in **Figures 1 and 2** provide insight into the effects of different classes of anticoagulants on hemostasis (**Figure 3**). Current anticoagulants either reduce plasma levels of prothrombin and FX (VKAs), or inhibit their activated forms (heparins and DOACs). Because thrombin and FXa are as important in the host response to injury as they are in thrombosis, their inhibition must compromise hemostasis to some extent if they are to be effective antithrombotic agents. However, this puts a limitation on the intensity of therapy that can be administered, and means that some patients with high bleeding risk will not be eligible for therapy. FXI, by contrast, serves an ancillary role in hemostasis, and its relative contributions to thrombosis appear to be disproportionately large. Because patients with severe FXI deficiency rarely have spontaneous bleeding and are not at increased risk for bleeding into the central nervous system or gastrointestinal tract, therapies targeting FXI or FXIa should be associated with a relatively low risk for serious bleeding.

EFFECT OF FXI OR FXIa INHIBITORS ON COAGULATION TESTS

Despite the observation of a minimal bleeding propensity in patients with congenital FXI deficiency, laboratory tests may, on the surface, appear to suggest otherwise. FXI is part of the traditional intrinsic pathway of coagulation that, along with FVIII, FIX, and FXII, initiates thrombin generation and clot formation in the activated partial thromboplastin time (aPTT) assay. Consequently, deficiency or inhibition of FXI/FXIa prolongs the aPTT, but does not affect the prothrombin time assay, which is used to assess coagulation initiated by the FVIIa/TF complex via the extrinsic pathway. Indeed, if FXI-directed therapy inhibits most of the protein's plasma activity, the aPTT may be prolonged to a greater extent than that observed in patients with severe hemophilia A or B. Although this may seem to indicate a significant defect in hemostasis, in practice, there is poor correlation between plasma FXI levels as determined by the aPTT and bleeding propensity. This apparent paradox reflects the fact that the aPTT requires FXI to initiate clot formation (the assay readout for the aPTT), a role which FXI does not perform *in vivo*. As shown in **Figure 1**, initiation of clotting *in vivo* is triggered by the FVIIa/TF complex, which is not measured by the aPTT assay. When required, FXI serves as a consolidator of coagulation *in vivo*, and

not as an initiator. This consolidating activity is not captured by the aPTT assay. In fact, no readily available coagulation assay accurately reflects the role of FXI in hemostasis. Therefore, when studying FXI or FXIa inhibitors, it is important to understand the limitations of the aPTT as an indicator of bleeding propensity even though it may be a good biomarker for presence of the drug.

CONCLUSIONS AND FUTURE DIRECTIONS

Current anticoagulation strategies are based on the premise that the enzymatic processes involved in hemostasis and thrombosis are similar. Following this approach, prevention of thrombosis requires inhibition of the hemostatic system, which increases the risk for bleeding. A substantial body of work over the past 20 years indicates that this notion, while intuitive, is an oversimplification. Plasma components such as FXI that have relatively small impacts on hemostasis make important contributions to thrombosis in humans and are, therefore, attractive targets for hemostasis-sparing therapies. Inhibition of FXI or FXIa has been effective at preventing VTE in phase 2 studies of patients undergoing total knee arthroplasty. Ongoing trials are assessing these agents for prevention of major adverse vascular events in patients with end-stage kidney disease undergoing hemodialysis or as adjuncts to antiplatelet therapy for prevention of recurrent ischemic events in patients with acute myocardial infarction or noncardioembolic stroke. Other studies are comparing FXI or FXIa inhibitors head to head with DOACs for stroke prevention in patients with atrial fibrillation. The results of these trials will not only establish the efficacy of FXI or FXIa inhibition, but will determine whether such an approach truly attenuates thrombosis with little or no disruption of hemostasis.

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