Making (Anti)Sense of Factor XI in Thrombosis
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Inhibiting thrombosis without inducing bleeding is the holy grail of anticoagulant therapy. Currently, there are no commercially available anticoagulants that achieve this goal. Although many antithrombotic agents improve survival by interfering with vessel thrombosis, this protection always comes at the cost of an increased risk of bleeding.

The observation that inhibitors of thrombosis increase bleeding is no surprise. Current dogma holds that the same blood constituents and mechanisms that are responsible for generating thrombin and fibrin to prevent excessive blood loss (hemostasis) can cause vessel stenosis or occlusion under pathologic conditions (thrombosis).

But what if this were not the case? Perhaps hemostasis and thrombosis are closely related but distinct processes, and perhaps factors can be identified that are essential for thrombosis but dispensable for hemostasis. As the study of clotting has moved from the test tube to animal models, increasing evidence has transformed this idea from fantasy to practicable hypothesis. Studies in factor XI knockdown mice have shown that these animals are protected from experimentally induced thrombosis without increased bleeding. In a primate model, antibodies directed at factor XI inhibited thrombus formation without affecting template bleeding times. Investigators have also used antisense oligonucleotides to target factor XI and have shown that reduction of factor XI levels provides protection from thrombosis in rabbits and primates, again with no increase in bleeding.

Büller et al. now report in the Journal the results of a study of an antisense oligonucleotide in humans. They conducted a phase 2 study involving 300 patients to evaluate the safety and efficacy of a factor XI antisense oligonucleotide for the prevention of deep-vein thrombosis after knee arthroplasty. Two regimens of the factor XI antisense oligonucleotide (200 mg and 300 mg) were compared with 40 mg of enoxaparin administered once daily, and venography to detect thrombosis was performed 8 to 12 days after surgery. The incidence of thrombosis did not differ significantly between the patients receiving enoxaparin and those receiving the 200-mg regimen of the antisense oligonucleotide (30% and 27%, respectively), with the 200-mg dose reducing factor XI levels by 68% of the baseline levels. Yet thrombosis was detected in only 4% of the patients receiving the 300-mg regimen, with that regimen reducing factor XI levels by 83%. Differences in the incidence of major bleeding among patients receiving the 200-mg dose of the factor XI antisense oligonucleotide (3%), those receiving the 300-mg dose of the factor XI antisense oligonucleotide (3%), and those receiving enoxaparin (8%) were not significant.

Do these findings prove that reduction of factor XI levels inhibits thrombosis without affecting bleeding? The conservative answer is no. Numerous other factors in addition to the levels of factor XI may contribute to this phenomenon. The incidence of clinically relevant bleeding is relatively low after knee arthroplasty, even when patients are receiving anticoagulants. Although the incidence of bleeding was increased in the enoxaparin group as compared with the group receiving the 300-mg dose of the factor XI antisense oligonucleotide, the difference was not significant. Furthermore, the incidence of clinically relevant bleeding that was observed with the 200-mg and 300-mg doses of the factor XI antisense oligonucleotide was within the range previously observed after prophylaxis with 40 mg of enoxaparin in patients undergoing knee arthroplasty (2 to 5%). A larger study will be required to evaluate whether targeting factor XI spares hemostasis.

These results also do not make a compelling
case for the clinical use of the factor XI antisense oligonucleotide over anticoagulants that are currently used for prophylaxis in patients undergoing knee arthroplasty. The investigators use bilateral venography to detect thrombosis. The incidence of venography-detected thrombosis is an order of magnitude higher than that of symptomatic venous thromboembolism, which was very low and did not differ significantly among the treatment groups in this study. A series of subcutaneous injections of factor XI antisense oligonucleotide was initiated 36 days before surgery and was associated with a high incidence of adverse events at the injection site. Furthermore, at 70 days after the initiation of treatment, factor XI levels remained reduced by approximately 60% without evidence of recovery. Issues of convenience and questions regarding reversibility might limit the use of factor XI antisense oligonucleotides for prophylaxis of venous thrombosis in patients undergoing surgery. Nonetheless, many conditions require long-term primary or secondary antithrombotic prophylaxis. Factor XI antisense oligonucleotide, with its prolonged activity and possibility of decreased bleeding risk, may represent a useful therapy in this context. This study also provides a compelling proof of principle for future trials of factor XI antisense oligonucleotides as well as for the intensification of ongoing efforts to develop small molecules and antibodies targeting factor XI.

Beyond these clinical implications, this study challenges the current paradigm that injury-induced exposure of tissue factor driving the generation of thrombin through the extrinsic pathway is the primary mechanism responsible for fibrin formation during thrombosis. The striking observation that reducing factor XI levels prevents thrombosis after knee arthroplasty provides the best clinical evidence to date that the intrinsic pathway is essential for thrombus formation.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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