EDITORIAL

How Effective and Safe Is Factor XI Inhibition in Preventing Venous Thrombosis?

Kenneth A. Bauer, MD

The introduction of the direct oral anticoagulants for stroke prevention in atrial fibrillation and the management of thromboembolism has transformed the care of patients with these disorders.[1] These drugs, which selectively and reversibly inhibit factor Xa or thrombin in the common pathway of the coagulation cascade, have a wide therapeutic window; this allows for simplified dosing regimens without laboratory monitoring of most adult patients as contrasted to vitamin K antagonists. This class of drug is also associated with a lower bleeding risk than vitamin K antagonists, which has been most clearly demonstrated by a 50% relative risk reduction in intracranial hemorrhage.[2] Nevertheless, bleeding with the direct oral anticoagulants remains a clinically significant issue, particularly in vulnerable patient populations, such as older patients and those with renal dysfunction.

Related article page 130

In the last 15 years, considerable interest has developed in targeting factor XII, a component of the contact activation pathway, and factor XI in the intrinsic coagulation cascade as an antithrombotic strategy. Studies have indicated that reductions in the activities of factor XII and factor XI can protect against the development of thrombosis in animal models.[3] Epidemiologic studies also have shown that patients with factor XI deficiency have a reduced risk of developing thrombotic complications.[4] As studies using a thrombosis model in nonhuman primates indicate that antibodies against factor XI may reduce platelet and fibrin deposition more effectively than those against factor XII,[5] this led to an initial focus on factor XI as a target for new anticoagulant development. The underlying premise is that these agents will be as effective as current anticoagulants, but with a significantly lower bleeding risk.

The strategies to inhibit factor XI include antisense oligonucleotide agents to reduce factor XI biosynthesis by the liver,[6] aptamers (short segments of DNA or RNA that bind to specific targets),[7] and monoclonal antibodies[8,9] or small molecules[10] that block its activation or activity. The first of these agents to be evaluated for its antithrombotic efficacy and bleeding safety was a factor XI–directed antisense oligonucleotide in a phase 3 trial of patients undergoing elective knee replacement.[6] A total of 300 patients were randomized to receive the agent subcutaneously at doses of 200 or 300 mg starting 35 days before surgery or a low-molecular-weight heparin (40 mg of enoxaparin) initiated at the time of surgery and continued for at least 8 days. The primary efficacy outcome was venous thromboembolism (VTE), which included asymptomatic deep venous thrombosis detected by venography, objectively confirmed symptomatic deep venous thrombosis or pulmonary embolism, and VTE-related mortality. The principal safety outcome was the composite of major and clinically relevant nonmajor bleeding. The 300-mg dose of the antisense oligonucleotide was more effective ($P < .001$) than enoxaparin in preventing VTE (4% [3 of 71] vs 30% [21 of 69], respectively), whereas the 200-mg dose of the antisense oligonucleotide met criteria for noninferiority. The rates of major and clinically relevant nonmajor bleeding were 3% in both antisense oligonucleotide groups and 8% in the enoxaparin group, a difference that was not statistically significant. Based on a comparison with enoxaparin, these results indicated that lowering factor XI levels to approximately 20% of normal reduced postoperative VTE without an increased bleeding risk.

Osocimab is a fully humanized IgG1 monoclonal antibody that reduces factor XIa activity and prolongs the activated partial thromboplastin time in a dose-dependent manner.[8] In this issue of *JAMA*, Weitz et al[11] report on the efficacy and safety of this antibody in a phase 2 trial involving 813 patients who had undergone elective total knee replacement. Osocimab was administered postoperatively in the first phase of the study. Based on the results, 2 doses of osocimab were given preoperatively. The efficacy and safety end points were similar to those in a previous trial that used a factor XI–directed antisense oligonucleotide.[6] The primary outcome was VTE up to 10 to 13 days postoperatively (assessed by mandatory venography) or confirmed symptomatic deep vein thrombosis or pulmonary embolism. A 5% noninferiority margin compared with enoxaparin was chosen. The primary safety outcome of major or clinically relevant nonmajor bleeding was also assessed until 10 to 13 days postoperatively. The results were compared with the administration of enoxaparin or the direct oral anticoagulant apixaban for at least 10 days or until the performance of venography. Venous thromboembolism occurred in 23.7% of patients receiving 0.3 mg/kg, 15.7% receiving 0.6 mg/kg, 16.5% receiving 1.2 mg/kg, and 17.9% receiving 1.8 mg/kg of osocimab. Doses higher than 0.3 mg/kg met criteria for noninferiority compared with enoxaparin (26.3%). Bleeding was observed in 2% of those receiving 0.3 mg/kg, 0% of those receiving 0.6 mg/kg, 1% receiving 1.2 mg/kg, and 3% of those receiving 1.8 mg/kg of osocimab. In the groups that received osocimab preoperatively, the VTE rates were 29.9% in the 0.3-mg/kg group and 11.3% in the 1.8-mg/kg group, the latter of which met criteria for superiority compared with enoxaparin; the bleeding rates were 1.9% and 4.7%, respectively.

For the early clinical evaluation of new anticoagulants, thromboprophylaxis following elective total knee replacement is a time-honored way to perform dose-finding studies with respect to efficacy and safety. It, however, has several limitations. First, the thrombotic end point in most patients is asymptomatic distal deep venous thrombosis, which is a surrogate for symptomatic thrombotic events; the latter, however, only occur in

a small fraction of patients with distal or even proximal deep venous thrombosis detected by bilateral venography. Symptomatic thrombotic events occurred in 0% to 2% in each cohort. Second, all patients in the study received an anticoagulant so that there was no placebo control group to assess the baseline rate of bleeding from the surgery. Adjudicated bleeding occurred in 0% to 3% at all dose levels, except for the group that received the highest antibody dose of 1.8 mg/kg of osocimab preoperatively; the bleeding rate was highest in this cohort at 4.7% (5 of 107). While the number of bleeding events was small and the results should not be overinterpreted, this group was also subjected to the most severe hemostatic challenge by having received the highest dose of antibody just prior to surgery.

Based on the results of this dose-finding study, it is not possible to conclude that the risk of bleeding using osocimab, the monoclonal antibody to factor XI, is less than that of currently available anticoagulants or to conclude that osocimab it is any more effective in preventing VTE than apixaban. The rate of bleeding in the group receiving the 1.8-mg/kg antibody dose preoperatively signals that a high degree of factor XI inhibition is not devoid of bleeding risk. Interestingly, the VTE and bleeding rates with apixaban were low at 12% and 2%, respectively.

It is clear that factor XII is not required for normal hemostasis, and individuals born with extremely low levels due to mutations in the gene encoding this coagulation factor do not have a bleeding diathesis. Unlike deficiencies of factor VIII and factor IX, individuals with factor XI deficiency rarely have spontaneous bleeding, hemarthrosis, or muscle hematomas. However, the premise that factor XI inhibition will not be associated with an increased risk of bleeding must be reconciled with the phenotype of individuals with hereditary factor XI deficiency in whom bleeding can occur following major surgery or trauma. The bleeding phenotype can be highly variable, and there is a poor correlation between plasma factor XI activity levels and bleeding.[12] Bleeding is most likely to occur in individuals with factor XI levels lower than 20% (homozygous or compound heterozygotes), but heterozygotes with factor XI activity levels higher than 20% may also have excessive surgical bleeding.[13,14]

The initial steps in hemostasis (ie, platelet plug formation and the early phase of thrombin generation in response to tissue factor exposure) are thought to occur normally in individuals with factor XI deficiency; only the subsequent amplification of thrombin generation and resistance of the clot to fibrinolysis are adversely affected by factor XI deficiency. The biological mechanism for the highly variable bleeding diathesis in patients with factor XI deficiency, however, is poorly understood.

Although the FOXTROT (Factor XIa Inhibition for the Prevention of Venous Thromboembolism in Patients Undergoing Total Knee Arthroplasty) clinical trial by Weitz et al[11] demonstrated that factor XI inhibition is effective in preventing VTE, osocimab, the monoclonal antibody used in this trial, was not safer than low-molecular-weight heparin or apixaban among patients following total knee replacement. Currently available antithrombotic agents including aspirin are widely used for this indication and demonstrate low rates of symptomatic VTE and bleeding.[15,16] However, older patients, those with renal dysfunction or those with prior major bleeding represent the high-risk populations who need safer anticoagulant agents. There is also an unmet need among acutely ill patients who require extracorporeal membrane oxygenation or left ventricular assist devices, where contact activation between artificial surfaces and the blood plays a major part in coagulation activation. Agents targeting factor XI or factor XII could prove to be particularly useful in these clinical settings. The trials of new anticoagulants in such high-risk populations, however, will be considerably more challenging to execute than those that led to the approval of the direct oral anticoagulants. The concerns regarding the reversal of bleeding following the introduction of the direct oral anticoagulants suggest that it will also be important to have reversal agents for inhibitors of factor XI available should these drugs gain regulatory agency approval.

ARTICLE INFORMATION

Author Affiliation: Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Kenneth A. Bauer, MD, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Boston, MA 02115 (kbauer@bidmc.harvard.edu).

Conflict of Interest Disclosures: Dr Bauer reported that he has served as a consultant for Janssen.

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