

ORIGINAL ARTICLE

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis

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ABSTRACT

BACKGROUND

Experimental data indicate that reducing factor XI levels attenuates thrombosis without causing bleeding, but the role of factor XI in the prevention of postoperative venous thrombosis in humans is unknown. FXI-ASO (ISIS 416858) is a second-generation antisense oligonucleotide that specifically reduces factor XI levels. We compared the efficacy and safety of FXI-ASO with those of enoxaparin in patients undergoing total knee arthroplasty.

METHODS

In this open-label, parallel-group study, we randomly assigned 300 patients who were undergoing elective primary unilateral total knee arthroplasty to receive one of two doses of FXI-ASO (200 mg or 300 mg) or 40 mg of enoxaparin once daily. The primary efficacy outcome was the incidence of venous thromboembolism (assessed by mandatory bilateral venography or report of symptomatic events). The principal safety outcome was major or clinically relevant nonmajor bleeding.

RESULTS

Around the time of surgery, the mean (\pm SE) factor XI levels were 0.38 ± 0.01 units per milliliter in the 200-mg FXI-ASO group, 0.20 ± 0.01 units per milliliter in the 300-mg FXI-ASO group, and 0.93 ± 0.02 units per milliliter in the enoxaparin group. The primary efficacy outcome occurred in 36 of 134 patients (27%) who received the 200-mg dose of FXI-ASO and in 3 of 71 patients (4%) who received the 300-mg dose of FXI-ASO, as compared with 21 of 69 patients (30%) who received enoxaparin. The 200-mg regimen was noninferior, and the 300-mg regimen was superior, to enoxaparin ($P<0.001$). Bleeding occurred in 3%, 3%, and 8% of the patients in the three study groups, respectively.

CONCLUSIONS

This study showed that factor XI contributes to postoperative venous thromboembolism; reducing factor XI levels in patients undergoing elective primary unilateral total knee arthroplasty was an effective method for its prevention and appeared to be safe with respect to the risk of bleeding. (Funded by Isis Pharmaceuticals; FXI-ASO TKA ClinicalTrials.gov number, NCT01713361.)

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*A complete list of investigators and study committees in the Factor XI-ASO Total Knee Arthroplasty study is provided in the Supplementary Appendix, available at NEJM.org.

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PATIENTS UNDERGOING TOTAL KNEE ARthroplasty are at risk for postoperative venous thromboembolism. Conventional therapies for the prevention of this complication involve inhibitors of factor Xa or thrombin, such as enoxaparin. These drugs are effective but are associated with a risk of bleeding.¹

The pathogenesis of venous thromboembolism after surgery is incompletely understood, but tissue factor exposed at the surgical site is thought to be the major driver through the extrinsic pathway of coagulation (Fig. 1).² The role of the intrinsic pathway in this process is uncertain.

Experimental data suggest that targeting factor XI, a key component of the intrinsic pathway, attenuates thrombosis without affecting hemostasis.³⁻⁶ Although the role of factor XI in throm-

bolism in humans is unknown, there is evidence that patients with congenital factor XI deficiency have a reduced risk of venous thromboembolism.⁷ They may, however, be prone to bleeding after serious trauma. Factor XI levels can be lowered with FXI-ASO (ISIS 416858), a 2'-O-(2-methoxyethyl) (2'-O-MOE) second-generation antisense oligonucleotide that specifically reduces human factor XI messenger RNA expression in the liver (Fig. 1).⁸

To determine whether lowering factor XI levels prevents venous thromboembolism without increasing the risk of bleeding, we compared several dose regimens of FXI-ASO with enoxaparin with respect to the rates of postoperative venous thromboembolism and bleeding in patients undergoing total knee arthroplasty.

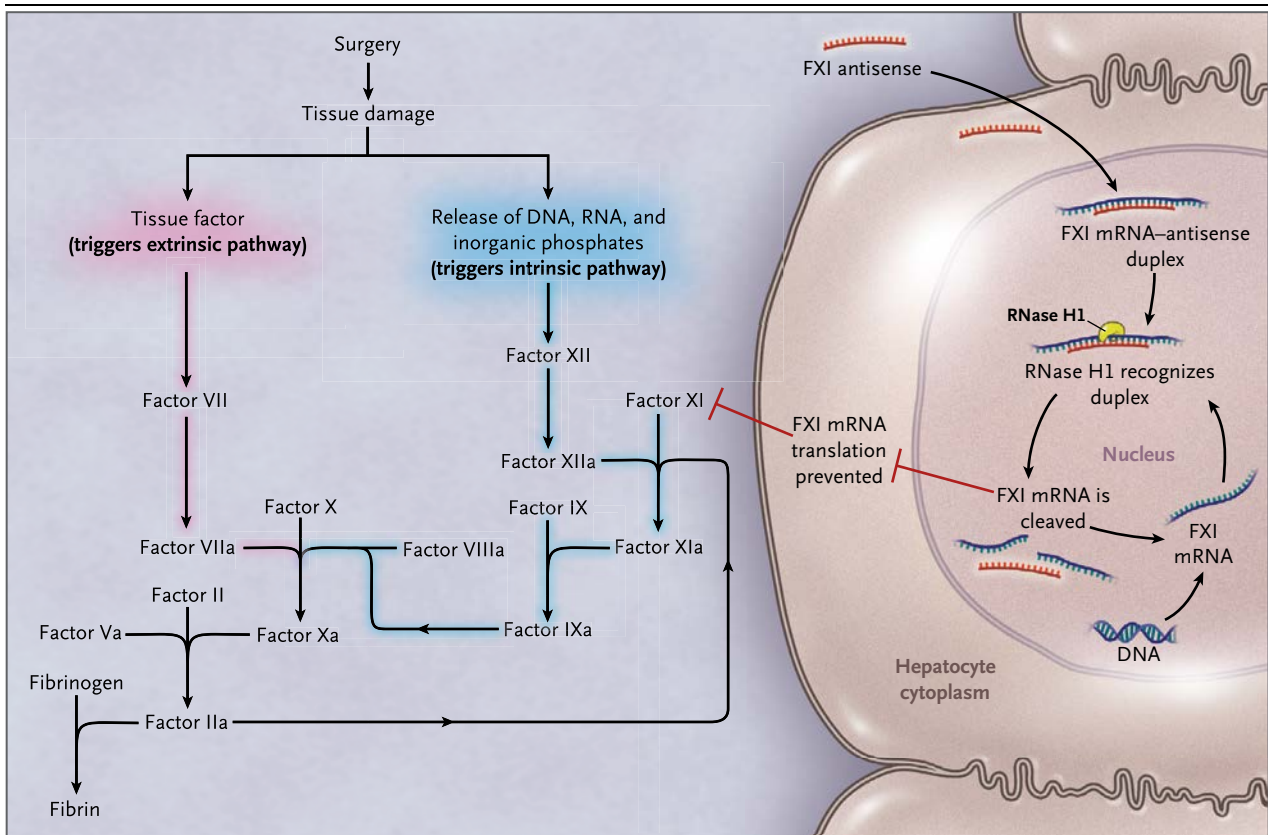


Figure 1. Effect of FXI-ASO on the Coagulation System.

FXI-ASO (ISIS 416858) is a factor XI (FXI)-targeted second-generation antisense oligonucleotide. Tissue damage after surgery exposes tissue factor and results in the release of DNA, RNA, and inorganic polyphosphate from damaged cells and from activated platelets and neutrophils. Tissue factor binds factor VIIa and initiates the extrinsic pathway of coagulation, whereas DNA, RNA, and polyphosphate activate factor XII and initiate the intrinsic pathway of coagulation. Factor XI-targeted antisense oligonucleotide attenuates the intrinsic pathway by binding to factor XI messenger RNA (mRNA) in the liver, which results in ribonuclease H1 (RNase H1)-mediated degradation of FXI messenger RNA, thereby preventing protein synthesis and reducing circulating FXI levels.

METHODS

STUDY DESIGN AND OVERSIGHT

In this phase 2, randomized trial, which had an open-label, parallel group, adaptive design, we compared three FXI-ASO dosing regimens (100 mg, 200 mg, and 300 mg) with 40 mg of enoxaparin. A steering committee in collaboration with the sponsor (Isis Pharmaceuticals) was responsible for the design and oversight of the study. The institutional review board at each participating center approved the protocol. All the patients provided written informed consent. The sponsor was responsible for the collection and maintenance of the data. An independent committee, whose members were unaware of the treatment assignments, adjudicated all venograms for the presence and extent of venous thrombosis, all clinically suspected episodes of venous thromboembolism or bleeding, and all cerebrovascular events. The authors wrote all drafts of the manuscript, verified the data, made the decision to submit the manuscript for publication, and vouch for the completeness of the data, the accuracy of the analyses, and the fidelity of the study to the protocol. The protocol and accompanying documents are available with the full text of this article at NEJM.org.

PATIENTS

Patients 18 to 80 years of age who were undergoing elective primary unilateral total knee arthroplasty and were willing to adhere to the study procedures were eligible for participation in the study. The main exclusion criteria were active bleeding or a high risk of bleeding, a history of brain or spinal surgery within the previous 3 months, anticipated use of intrathecal or epidural catheters, body weight below 50 kg, calculated creatinine clearance below 60 ml per minute, clinically significant liver disease, and venous thromboembolism within the previous year. The full list of exclusion criteria is provided in the protocol.

RANDOMIZATION AND STUDY TREATMENT

The initial protocol called for random assignment of patients to one of three dose regimens of FXI-ASO (100 mg, 200 mg, or 300 mg) or enoxaparin (Fig. 2). After 14 patients had undergone randomization, the steering committee amended

the protocol to discontinue the 100-mg dose regimen and to add to the 200-mg and 300-mg regimens two additional doses of FXI-ASO before surgery and one additional dose after surgery. This decision was made to ensure a sufficient reduction in factor XI levels during and after surgery. In this article, we report results from the amended protocol (Fig. 2), in which patients were randomly assigned to one of two regimens of FXI-ASO (200 mg or 300 mg) and within each regimen to receive treatment with either FXI-ASO or enoxaparin in a 3:1 ratio (for a more detailed description of the randomization procedure, see the Supplementary Appendix, available at NEJM.org).

Treatment with FXI-ASO was initiated 36 days before surgery (day 1 of the study). Patients received three subcutaneous doses of FXI-ASO during the first week of treatment (days 1, 3, and 5) followed by four once-weekly doses on days 8, 15, 22, and 29. On day 36, the day of surgery, patients received a dose 6 hours postoperatively. A final dose was given on day 39 (Fig. S1 in the Supplementary Appendix).

Enoxaparin, at a dose of 40 mg administered subcutaneously once daily, was initiated the evening before or 6 to 8 hours after surgery, according to the investigator's preference, and was to be continued for at least 8 days postoperatively.

STUDY OUTCOMES

The primary efficacy outcome was the incidence of adjudicated total venous thromboembolism, which was a composite of asymptomatic deep-vein thrombosis (detected by mandatory bilateral venography), objectively confirmed symptomatic venous thromboembolism, fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out. Venography was to be performed 8 to 12 days after the surgery.

Prespecified secondary efficacy outcomes included the individual components of the primary efficacy outcome. An exploratory outcome was the extent of venous thrombosis on venography, as assessed by the adjudication committee according to prespecified categories of bilateral thrombosis, confluent distal-to-proximal thrombosis, isolated proximal deep-vein thrombosis classified as large (≥ 10 cm) or small (< 10 cm), and isolated distal deep-vein thrombosis classified as extensive (≥ 2 veins) or limited (< 2 veins).

The principal safety outcome was the incidence

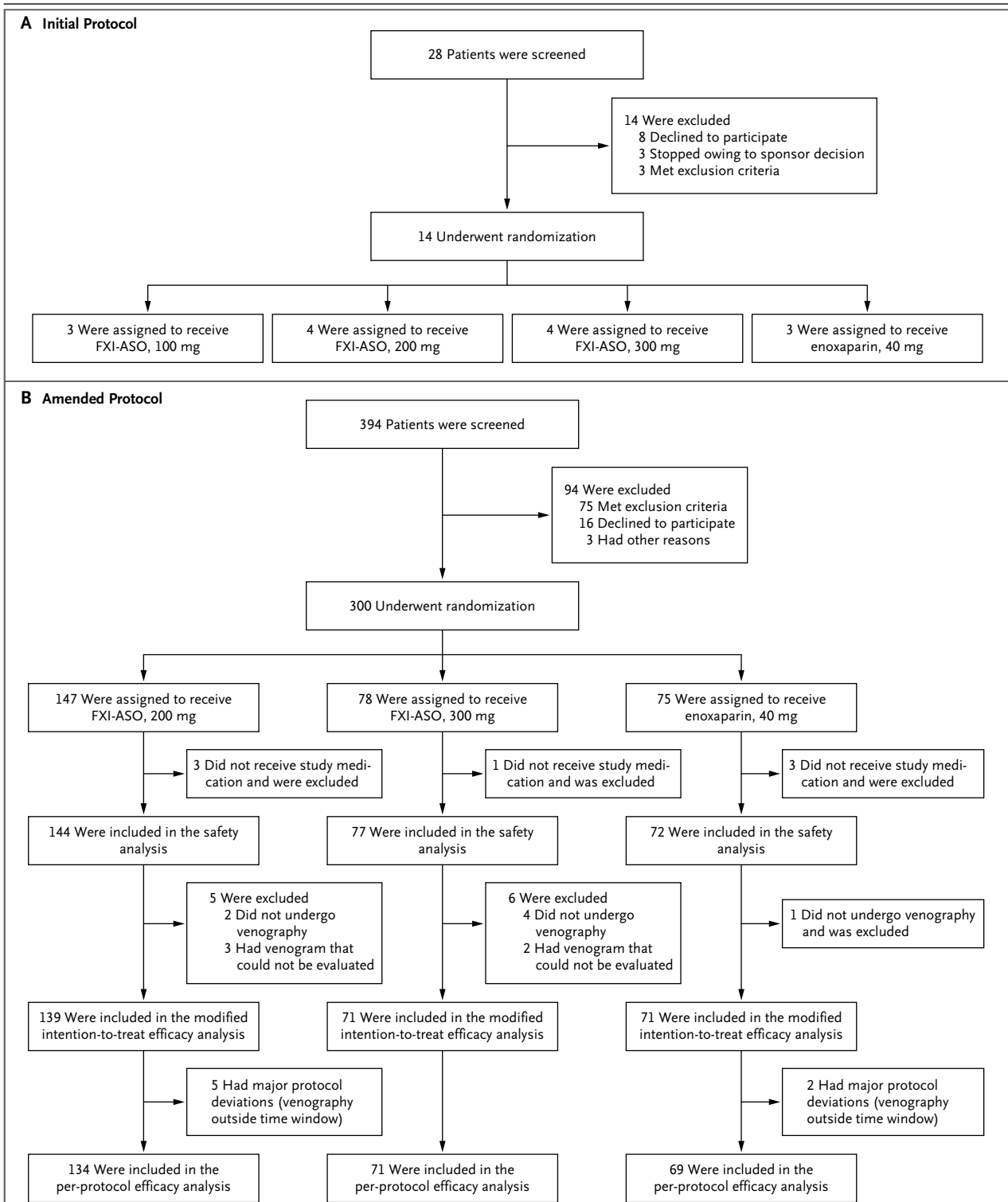


Figure 2. Enrollment, Randomization, and Populations for Analysis.

The initial protocol (Panel A) called for random assignment of patients to one of three dose regimens of FXI-ASO (100 mg, 200 mg, or 300 mg) or enoxaparin. After 14 patients had undergone randomization, the steering committee amended the protocol (Panel B) to discontinue the 100-mg dose regimen. Random assignment to the 300-mg FXI-ASO cohort was discontinued when the target sample of 70 patients was recruited in that group. Enrollment was continued in the 200-mg cohort until the study ended.

of adjudicated clinically relevant bleeding, which was a composite of major or clinically relevant nonmajor bleeding. Bleeding was defined as major if it was overt and if it was associated with a decrease in hemoglobin of 2 g per deciliter or necessitated transfusion of 2 or more units of blood, occurred in a critical area or organ, or was fatal. Bleeding at the surgical site was defined as major only if it required an intervention or caused hemarthrosis that delayed wound healing or mobilization, prolonged hospitalization, or was associated with deep wound infection.⁹ Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but required intervention or consultation with a physician or had clinical consequences¹⁰ (details are provided in the Supplementary Appendix). All other clinically overt bleeding events were classified as minor. Other safety outcomes included adverse events, abnormal results on liver-function tests, cardiovascular events, and deaths.

Pharmacodynamic outcomes included changes in the activated partial-thromboplastin time and factor XI levels, as measured in a central laboratory. Activated partial-thromboplastin times were determined with the use of standard two-stage assays. Ratios were established by dividing the results of those assays by the mean of the normal control. Factor XI activity was determined with the use of factor XI-depleted plasma. The reference value, which was derived from control plasma, was 1.0 unit per milliliter.

SURVEILLANCE AND FOLLOW-UP

Patients receiving FXI-ASO were evaluated at the time of each preoperative injection, whereas surveillance of patients in the enoxaparin group started with the first dose on the evening before or the day of surgery. All the patients were assessed every day postoperatively until venography was performed and were followed according to a prespecified schedule for 3 months thereafter. Patients were instructed to report symptoms that were suggestive of venous thromboembolism or bleeding.

STATISTICAL ANALYSIS

The study was designed to evaluate the safety and efficacy of FXI-ASO as compared with enoxaparin according to dose regimen and according to the average factor XI levels (≤ 0.2 vs. > 0.2 units per milliliter) between day 36 and day 39 (i.e., the perioperative period). The rationale for this cut-

off was based on clinical and experimental observations.^{3,6,7}

The safety population included all patients who received at least one dose of study medication. The modified intention-to-treat population consisted of all patients in the safety population who could be evaluated for the primary efficacy outcome. The per-protocol population comprised all patients in the modified intention-to-treat population, excluding those with major protocol violations (Fig. 2).

The primary efficacy analysis tested the hypothesis that FXI-ASO would be noninferior to enoxaparin among patients in the per-protocol population who had average factor XI levels of 0.2 units per milliliter or less between day 36 and day 39 of treatment; the analysis included all events up to 12 days postoperatively. We prespecified that noninferiority would be shown if the upper limit of the 90% confidence interval for the between-group difference in risk was 14% or less. If noninferiority was shown, superiority testing would be performed with the use of the chi-square test or Fisher's exact test, as appropriate. We calculated that with 70 patients in each group, the study would have 80% power to show noninferiority. This calculation assumed rates of 18% for the primary efficacy outcome in all treatment groups. The noninferiority margin was chosen to be the midpoint of the 27-percentage-point difference in risk between the rate with placebo (45%) and the expected treatment rate (18%).¹¹ This margin corresponds to retention of about 50% of the treatment effect of enoxaparin.

Secondary efficacy analyses compared the rates of the components of the primary efficacy outcome among the treatment groups. These analyses were repeated with the inclusion of events up to 4 weeks after venography. We also performed a sensitivity analysis of efficacy using the modified intention-to-treat population and an exploratory analysis of the extent of thrombosis. Analysis of the principal safety outcome and its components was performed in the safety population and included all events during study treatment and follow-up until day 136.

RESULTS

PATIENTS

From July 2013 through March 2014, a total of 300 patients at 19 centers in five countries underwent randomization according to the amend-

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	FXI-ASO, 200 mg (N=144)	FXI-ASO, 300 mg (N=77)	Enoxaparin, 40 mg (N=72)
Age — yr	63±9	63±8	64±9
Female sex — no. (%)	118 (82)	60 (78)	60 (83)
Weight — kg			
Mean	89	90	87
Range	52–124	52–130	52–132
Creatinine clearance — ml/min	112±31	116±30	111±30
Duration of surgery — hr	1.8±0.7	1.9±0.8	1.9±0.8
Time to ambulation — hr	35±19	39±21	39±20
Length of hospital stay — days	15±5	14±5	16±5
Type of anesthesia received — no. of patients†			
General	138	72	64
Spinal	4	1	7
Activated partial-thromboplastin time ratio	0.97±0.11	0.95±0.09	0.95±0.11
Factor XI activity — units/ml	1.20±0.20	1.16 ±0.22	1.23±0.21
Duration of enoxaparin treatment — days			
Median	—	—	10
Interquartile range			10–10
Proportion of prescribed injections of FXI-ASO received — %	97	92	—

* Plus-minus values are means ±SD. The characteristics listed here were assessed in the safety population, which included all patients who received at least one dose of study medication. There were no clinically important differences among the treatment groups in any of the listed characteristics. There were also no statistically significant between-group differences, with the exception of the type of anesthesia received, with more patients in the enoxaparin group than in the FXI-ASO groups receiving spinal anesthesia (P=0.02).

† Not all patients in the safety population underwent surgery.

Table 2. Efficacy and Safety Outcomes.*

Outcome	FXI-ASO, 200 mg (N=134)	FXI-ASO, 300 mg (N=71)	Enoxaparin, 40 mg (N=69)
Efficacy			
Primary efficacy outcome: total venous thromboembolism — no. (% [95% CI])†	36 (27 [20 to 35])	3 (4 [1 to 12])	21 (30 [20 to 43])
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 90% CI)	-4 (5)	-26 (-18)	—
Risk difference, FXI-ASO vs. enoxaparin — % (upper limit of 95% CI)	-4 (8)	-26 (-16)	—
P value for superiority of FXI-ASO to enoxaparin	0.59	<0.001	—
Secondary efficacy outcomes: components of the primary efficacy outcome — no. (%)			
Symptomatic venous thromboembolism	2 (1)	0	1 (1)
Asymptomatic deep-vein thrombosis	34 (25)	3 (4)	20 (29)
Proximal deep-vein thrombosis	7 (5)	1 (1)	4 (6)
Distal deep-vein thrombosis	29 (22)	2 (3)	17 (25)
Exploratory efficacy outcome: extent of venous thrombosis on venography			
Patients with deep-vein thrombosis — no. (%)	36 (27)	3 (4)	21 (30)
Extent of deep-vein thrombosis — no.			
Bilateral‡	2	0	2
Confluent distal into proximal	6	0	2
Isolated proximal			
Large: ≥10 cm	0	0	1
Small: <10 cm	0	1	0
Isolated distal			
Extensive: ≥2 veins	16	0	7
Limited: <2 veins	12	2	9

Table 2. (Continued.)

Outcome	FXI-ASO, 200 mg (N=144)	FXI-ASO, 300 mg (N=77)	Enoxaparin, 40 mg (N=72)
Safety§			
Principal safety outcome: major or clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	2 (3 [<1 to 9])	6 (8 [3 to 17])
Risk difference, FXI-ASO vs. enoxaparin — % (95% CI)	-6 (-12 to 1)	-6 (-13 to 2)	
P value by Fisher's exact test, FXI-ASO vs. enoxaparin	0.09	0.16	
Major bleeding — no. (% [95% CI])¶	0 [0 to 2.5]	1 (1 [<1 to 7])	0 [0 to 5.0]
Clinically relevant nonmajor bleeding — no. (% [95% CI])	4 (3 [1 to 7])	1 (1 [<1 to 7])	6 (8 [3 to 17])
Receipt of blood transfusion — no. (%)	55 (38)	22 (29)	23 (32)
Adverse events — no. of patients (%)			
≥1 adverse event	114 (79)	62 (81)	47 (65)
Serious adverse event	3 (2)	1 (1)	0
Any adverse event resulting in permanent discontinuation of study drug**	1 (1)	1 (1)	0
Injection-site-related adverse event††	32	25	2

* Efficacy outcomes were assessed in the per-protocol efficacy population, which comprised all patients who received at least one dose of study medication and who could be evaluated for the primary efficacy outcome, with the exclusion of patients with major protocol violations. Safety outcomes were assessed in the safety population, which included all patients who received at least one dose of study medication. CI denotes confidence interval.

† Total venous thromboembolism was a composite of asymptomatic deep-vein thrombosis (detected by mandatory bilateral venography), objectively confirmed symptomatic venous thromboembolism, fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out. None of the patients had a pulmonary embolism.

‡ In the 200-mg FXI-ASO group, one patient had bilateral distal deep-vein thrombosis and one patient had distal deep-vein thrombosis confluent to the popliteal vein in the right leg and distal deep-vein thrombosis alone in the left leg; in the enoxaparin group, one patient had bilateral distal deep-vein thrombosis and one patient had bilateral distal deep-vein thrombosis confluent to the proximal veins.

§ The safety outcomes reported here include data from the first administration of the study drug to study day 136 (end of the study). The observation period in the FXI-ASO groups was longer than that with enoxaparin because the FXI-ASO injections were started on day 1 (36 days before surgery) and continued to day 39 (3 days after surgery), and patients in the 300-mg group received two injections per dosing. In the enoxaparin group, the injections started on the day of surgery or the day before.

¶ One episode of surgical-site hematoma requiring drainage occurred in a patient in the 300-mg FXI-ASO group.

|| In the 200-mg FXI-ASO group, the serious adverse events were transient ischemic attack (in one patient), fistula of the postoperative scar (in one patient), and ligature fistula (in one patient); in the 300-mg FXI-ASO group, one patient had a periprosthetic infection. All these events were considered by the investigators as unlikely to be related or as unrelated to FXI-ASO therapy.

** The reasons for discontinuation were itching and worsening of preexisting arterial hypertension (one patient in the 200-mg FXI-ASO group) and bleeding from the surgical site (one patient in the 300-mg FXI-ASO group).

†† Injection-site adverse events included one or more of the following: erythema, pain, pruritus, swelling, and hematoma.

ed protocol. The analysis populations are shown in Figure 2. The baseline characteristics were similar in the three study groups (Table 1).

EFFICACY

Venograms that could be evaluated were obtained in 281 of the 293 patients (96%) who received study medication (Fig. 2). Seven of the patients whose venograms could be evaluated underwent venography outside the 8-to-12-day postoperative period, and only 1 (in the enoxaparin group) had deep-vein thrombosis. These 7 patients were excluded from the per-protocol population. There were no other major protocol violations.

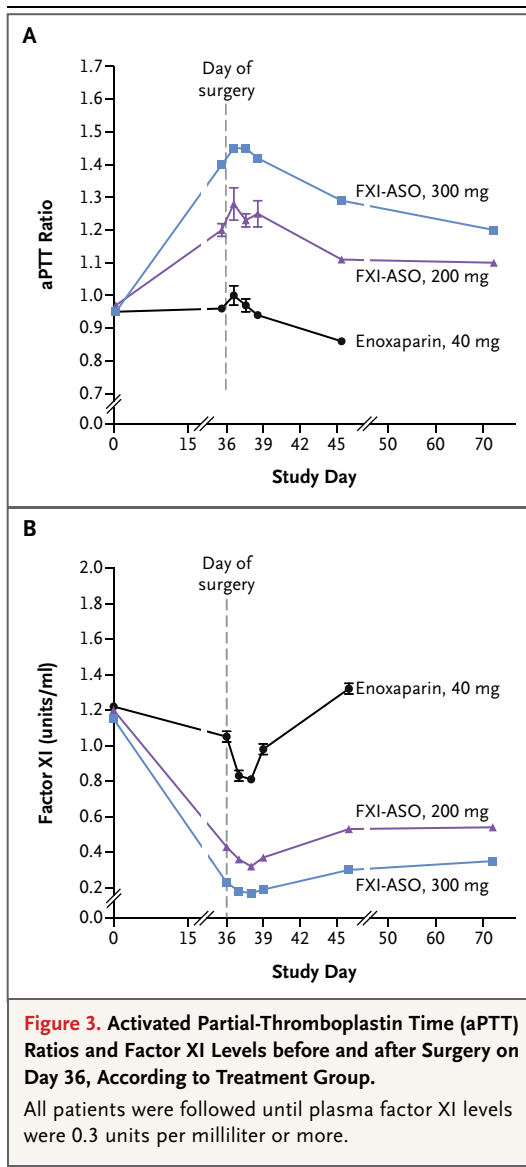
In the per-protocol population, the primary efficacy outcome occurred in 36 of 134 patients (27%) in the 200-mg FXI-ASO group, in 3 of 71 patients (4%) in the 300-mg FXI-ASO group, and in 21 of 69 patients (30%) in the enoxaparin

group. The modified intention-to-treat analysis yielded similar results (Table S1 in the Supplementary Appendix).

Both FXI-ASO regimens met the prespecified criteria for noninferiority, and the 300-mg FXI-ASO regimen was superior to enoxaparin (P<0.001) (Table 2). In the group of patients who had an average factor XI level of 0.2 units per milliliter or lower, the incidence of the primary efficacy outcome was 5% (for additional details, see Table S2 in the Supplementary Appendix). No patient had a symptomatic pulmonary embolism, and no patient had symptomatic deep-vein thrombosis in the follow-up period after venography. There were no deaths.

BLEEDING

The principal safety outcome of clinically relevant bleeding occurred in 4 of 144 patients (3%)



in the 200-mg FXI-ASO group, in 2 of 77 patients (3%) in the 300-mg FXI-ASO group, and in 6 of 72 patients (8%) in the enoxaparin group (Table 2). The results for major bleeding, clinically relevant nonmajor bleeding, and blood transfusions are provided in Table 2. The preoperative and postoperative hemoglobin values were similar in the three treatment groups (Fig. S2 in the Supplementary Appendix)

OTHER SAFETY OUTCOMES

The rates of adverse events are shown in Table 2. The study drug was discontinued in two patients because of an adverse event. Although injection-site reactions were frequently observed with FXI-

ASO, these reactions were mild and did not result in discontinuation of the study drug. No patient met the criteria for abnormal liver-function tests during treatment with FXI-ASO preoperatively; two patients in the 200-mg FXI-ASO group had transient increases in the alanine aminotransferase level postoperatively.

ACTIVATED PARTIAL-THROMBOPLASTIN TIME RATIOS AND INTRINSIC FACTOR LEVELS

The activated partial-thromboplastin time ratios and factor XI levels are shown in Figure 3. The mean (\pm SE) levels of factor XI during days 36 to 39 were 0.38 ± 0.01 units per milliliter in the 200-mg FXI-ASO group, 0.20 ± 0.01 units per milliliter in the 300-mg FXI-ASO group, and 0.93 ± 0.02 units per milliliter in the enoxaparin group. The levels of factors VIII, IX, and XII were similar in the three treatment groups, as were the prothrombin time ratios (data not shown).

DISCUSSION

This study showed that the 200-mg dose regimen of FXI-ASO was noninferior to enoxaparin for the prevention of venous thromboembolism, and the 300-mg dose regimen was superior to enoxaparin, with rates of venous thromboembolism of 30% in the enoxaparin group, 27% in the 200-mg FXI-ASO group, and 4% in the 300-mg FXI-ASO group. The rate of major or clinically relevant nonmajor bleeding was lower with the 300-mg dose regimen than with enoxaparin (3% vs. 8%), a difference that did not reach statistical significance. The safety of this dose regimen is supported by the fact that postoperative hemoglobin levels with FXI-ASO were similar to those with enoxaparin, even though around the time of surgery the mean factor XI level in the 300-mg FXI-ASO group was reduced to 0.20 ± 0.01 units per milliliter and the mean activated partial-thromboplastin time ratio was increased to 1.4 ± 0.02 . Therefore, this study showed that factor XI contributes to postoperative venous thromboembolism and that lowering factor XI levels was an effective method for its prevention and appeared to be safe.

FXI-ASO influenced only the intrinsic pathway, as evidenced by the prolongation of the activated partial-thromboplastin time with no effect on the prothrombin time. It lowered factor XI levels in a dose-dependent fashion, whereas the levels of factors VIII, IX, and XII, the other

components of the intrinsic pathway, were unaffected — findings that highlight the specificity of FXI-ASO.

The finding that lowering the level of factor XI reduced the rate of venous thromboembolism after surgery challenges the concept that tissue factor is the main driver of thrombosis among patients undergoing surgery.² In fact, our observation that the 300-mg dose regimen of FXI-ASO markedly reduced the rate of venous thrombosis, as compared with enoxaparin, and that any clots that formed were small, raises the possibility that factor XI may be involved not only in the propagation of thrombosis, but also in its initiation. Factor XI can be activated by thrombin or by factor XIIIa.^{12,13} Factor XII can be activated during surgery because activators, such as DNA, RNA, and polyphosphates, are released from damaged tissue and activated neutrophils or platelets (Fig. 1).¹³⁻¹⁵ Regardless of whether factor XI is activated by factor XIIIa or by thrombin, reducing factor XI levels will attenuate thrombosis. Therefore, factor XI is an attractive target for antithrombotic therapy.

Some methodologic aspects of our study require comment. First, the strength of our conclusion regarding bleeding is limited by the modest sample size. Although additional studies are needed to confirm the safety of FXI-ASO, the

fact that patients receiving this therapy safely underwent major orthopedic surgery is reassuring. Second, although the study was open-label, all outcomes were adjudicated by a committee whose members were unaware of the treatment assignments. Third, although we used 0.2 units per milliliter as a prespecified cutoff for the factor XI level, the range required to achieve the most effective antithrombotic effect is unknown. Our results, together with epidemiologic data,^{16,17} suggest that there is such a range, but additional studies are needed to identify it. Finally, although the slow onset of action of FXI-ASO precludes its use as the sole therapy when a rapid antithrombotic effect is needed, its profile renders it an appealing option for the management of a wide range of chronic thrombotic conditions.

In summary, FXI-ASO has the potential to reduce the rate of postoperative thrombosis to a greater extent than conventional anticoagulants, without increasing bleeding. These findings support the concept that with the use of strategies targeting factor XI, thrombosis and hemostasis can be dissociated.

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

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