Original Article

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Abelacimab for Prevention of Venous Thromboembolism

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*A complete list of investigators and committees in the ANT-005 TKA (Total Knee Arthroplasty) trial is provided in the Supplementary Appendix, available at NEJM.org.

Abstract

Background

The role of factor XI in the pathogenesis of postoperative venous thromboembolism is uncertain. Abelacimab is a monoclonal antibody that binds to factor XI and locks it in the zymogen (inactive precursor) conformation.

Methods

In this open-label, parallel-group trial, we randomly assigned 412 patients who were undergoing total knee arthroplasty to receive one of three regimens of abelacimab (30 mg, 75 mg, or 150 mg) administered postoperatively in a single intravenous dose or to receive 40 mg of enoxaparin administered subcutaneously once daily. The primary efficacy outcome was the incidence of venous thromboembolism, detected by mandatory venography of the leg involved in the operation or objective confirmation of symptomatic events. The principal safety outcome was a composite of major or clinically relevant nonmajor bleeding up to 30 days after surgery.

Results

Venous thromboembolism occurred in 13 of 102 patients (13%) in the 30-mg abelacimab group, 5 of 99 patients (5%) in the 75-mg abelacimab group, and 4 of 98 patients (4%) in the 150-mg abelacimab group, as compared with 22 of 101 patients (22%) in the enoxaparin group. The 30-mg abelacimab regimen was noninferior to enoxaparin, and the 75-mg and 150-mg abelacimab regimens were superior to enoxaparin ($P<0.001$). Bleeding occurred in 2%, 2%, and none of the patients in the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, and in none of the patients in the enoxaparin group.

Conclusions

This trial showed that factor XI is important for the development of postoperative venous thromboembolism. Factor XI inhibition with a single intravenous dose of abelacimab after total knee arthroplasty was effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding. (Funded by Anthos Therapeutics; ANT-005 TKA EudraCT number, 2019-003756-37).

Patients undergoing total knee arthroplasty are at high risk for postoperative venous thromboembolism. Enoxaparin, an inhibitor of factor Xa and thrombin, is often administered postoperatively to reduce this risk. Although reasonably effective, enoxaparin can be associated with bleeding. A search for safer and more effective anticoagulants is under way.

Tissue factor exposed at the surgical site is considered to be the main driver of postoperative venous thromboembolism through the extrinsic pathway of coagulation.[1] The importance of the intrinsic pathway in the pathogenesis of postoperative venous thrombosis is uncertain. Emerging evidence suggests that targeting factor XI, a key component of the intrinsic pathway, attenuates thrombosis with little disruption of hemostasis. Patients with congenital factor XI deficiency are at lower risk for venous thromboembolism than patients with normal factor XI levels, and they rarely have spontaneous bleeding.[2,3]

When administered preoperatively (starting 35 days before total knee arthroplasty), an antisense oligonucleotide that induces knockdown of factor XI was associated with a significantly lower risk of postoperative venous thromboembolism than enoxaparin, without increasing the risk of bleeding.[4] In contrast, when administered postoperatively, osocimab (a monoclonal antibody that inhibits factor XIa) was noninferior to enoxaparin for the prevention of venous thromboembolism after total knee arthroplasty; osocimab was superior to enoxaparin only when administered preoperatively.[5] Therefore, whether postoperative factor XI inhibition is as effective as preoperative inhibition remains unknown.

Abelacimab (MAA868) is a fully human monoclonal antibody that binds to the catalytic domain of factor XI and locks it in the zymogen (inactive precursor) conformation, thereby preventing its activation by factor XIIa or thrombin.[6] The intravenous infusion of abelacimab almost immediately reduces the functional factor XI level in a dose-dependent manner. We compared the efficacy and safety of abelacimab administered postoperatively with the efficacy and safety of enoxaparin in patients undergoing total knee arthroplasty.

Methods

Trial Design and Oversight

In this phase 2, prospective, randomized, parallel-group trial, we compared three regimens of abelacimab (30 mg, 75 mg, or 150 mg) with enoxaparin. Assignment to enoxaparin or abelacimab was conducted in an open-label

manner; assignment to an abelacimab regimen was conducted in a blinded manner. A steering and safety committee in collaboration with the sponsor (Anthos Therapeutics) was responsible for the design and oversight of the trial. 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 trial-group assignments, adjudicated all venograms for the presence and extent of venous thrombosis and adjudicated all suspected episodes of symptomatic venous thromboembolism or bleeding. The first, third, and last authors wrote the first draft of the manuscript with input from the other authors. The authors wrote all drafts of the manuscript, verified the data, and vouch for the completeness of the data, the accuracy of the analyses, and the fidelity of the trial to the protocol. No one who is not an author contributed to writing the manuscript. 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, had a body weight of 50 to 130 kg, and were willing to adhere to the trial procedures were eligible for participation in the trial. The main exclusion criteria were active bleeding or a high risk of bleeding, a history of venous thromboembolism, an estimated glomerular filtration rate below 60 ml per minute per 1.73 m^2 of body-surface area (amended to a rate below 45 ml per minute per 1.73 m^2), and clinically significant liver disease. The full list of inclusion and exclusion criteria is provided in the protocol.

Randomization and Trial Interventions

Before surgery, patients were randomly assigned in a 1:1:1:1 ratio to receive one of three regimens of abelacimab (30 mg, 75 mg, or 150 mg) or enoxaparin (Fig. 1). Randomization was stratified according to trial center. Abelacimab, administered in a single intravenous infusion over a period of 30 to 60 minutes, was started 4 to 8 hours after surgery. Enoxaparin, at a dose of 40 mg administered subcutaneously once daily, was started either the evening before or approximately 12 hours after surgery and was to be continued until venography was performed. The dosage for enoxaparin was based on the standard of care in the countries in which the trial was conducted.

Trial Outcomes

The primary efficacy outcome was the incidence of adjudicated venous thromboembolism, defined as a composite of asymptomatic deep-vein thrombosis (detected by mandatory unilateral ascending venography performed after surgery, between day 8 and day 12), confirmed symptomatic venous thromboembolism (symptomatic deep-vein thrombosis of the leg or nonfatal pulmonary embolism), fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out. Unilateral venography, performed only on the leg involved in the operation, detects more than 90%

of cases of deep-vein thrombosis in patients undergoing unilateral knee arthroplasty[4,7] while avoiding the risks associated with bilateral venography. An exploratory efficacy outcome was the extent of venous thrombosis on venography, which was assessed by the adjudication committee according to prespecified categories.

The principal safety outcome was the incidence of adjudicated clinically relevant bleeding, defined as a composite of major or clinically relevant nonmajor bleeding, from randomization until venography was completed and from randomization through day 30. An exploratory safety outcome was the incidence of adjudicated clinically relevant bleeding from randomization through day 110. Major bleeding was defined as overt bleeding that was associated with a decrease in the hemoglobin level of 2 g per deciliter or more or necessitated transfusion of 2 units of blood or more within 48 hours, occurred in a critical area or organ, or was fatal. Bleeding at the surgical site was classified as major only if it resulted in an intervention, caused hemodynamic instability, or caused hemarthrosis that delayed mobilization or wound healing and resulted in prolonged hospitalization or deep wound infection.[8] Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but resulted in a medical examination or an intervention or had clinical consequences (details are provided in the Supplementary Appendix, available at NEJM.org).

Monitoring for adverse events included assessment for hypersensitivity and infusion-related reactions. Hemoglobin levels and the frequency of blood transfusions were evaluated as exploratory safety variables.

The activated partial-thromboplastin time and plasma concentration of abelacimab were determined before surgery and after surgery on days 3, 10, 30, 50, and 110; Covid-19 restrictions precluded collection of samples from some patients on day 50. The activated partial-thromboplastin time was determined at a central laboratory with the use of Actin FSL (Covance Central Laboratory Services, Indianapolis); ratios were calculated by dividing postoperative values by preoperative values. Factor XI activity and the free factor XI level, which indicates the concentration of factor XI without bound abelacimab, were quantified before surgery and after surgery on days 3, 10, and 30, as described previously.[6]

Surveillance and Follow-up

Patients were evaluated the day before surgery and after surgery on days 1, 3, 6, and 10 and were contacted on days 30, 50, and 110. Patients were instructed to report symptoms that were suggestive of venous thromboembolism or bleeding.

Statistical Analysis

The primary efficacy analysis tested the hypothesis that abelacimab would be noninferior to enoxaparin for the prevention of venous thromboembolism after surgery (with venography performed between day 8 and day 12). We prespecified that noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the incidence of

postoperative venous thromboembolism was less than 14 percentage points. This noninferiority margin was chosen to preserve approximately 50% of the placebo-adjusted benefit of enoxaparin.[9]

We calculated that with 150 patients in each trial group, the trial would have 80% power to show noninferiority, with a one-sided alpha level of 2.5% for each comparison. This calculation assumed an incidence of 25% for the primary efficacy outcome in all trial groups and a hierarchical approach to testing. Therefore, the planned sample size was 600 patients. However, the steering and safety committee and the sponsor elected to stop randomization on November 24, 2020, anticipating that 100 patients per trial group would have undergone randomization at that time. This decision was driven by slowed recruitment because of the coronavirus disease 2019 pandemic, with resultant impending expiration of trial drugs. No interim analyses or reassessments of sample size were undertaken.

The stratified Cochran–Mantel–Haenszel test was used to assess the null hypothesis that the upper limit of the 95% confidence interval for the between-group difference in the incidence would be equal to or greater than the noninferiority margin, as compared with the alternative hypothesis that the upper limit would be less than the noninferiority margin, with an overall one-sided alpha level of 2.5%. The 95% confidence interval for the between-group difference in the incidence was calculated with the use of weights that were based on the randomization strata. For noninferiority testing, multiplicity was controlled with the use of a hierarchical step-down procedure; the high, medium, and low doses of abelacimab were compared with enoxaparin in that order. Subsequent superiority testing was conducted for doses that showed noninferiority, with the use of a one-sided alpha level of 2.5% for the null hypothesis. Superiority testing had no effect on the family-wise type I error rate because the noninferiority and superiority assessments were part of the same closed test.[10]

The primary efficacy analysis was performed in the modified intention-to-treat population, which consisted of all patients who received at least one dose of trial medication and could be evaluated for the primary efficacy outcome. Secondary efficacy analyses were based on events that occurred through day 30 and through day 110 in the modified intention-to-treat population and in the per-protocol population, which consisted of all patients in the modified intention-to-treat population who had no major deviations from the protocol (details are provided in the Supplementary Appendix). The analysis of the principal safety outcome and its components was performed in the safety population, which consisted of all patients who received at least one dose of trial medication.

Results

Patient Characteristics

From June 2020 through November 2020, a total of 412 patients at 16 centers in five countries underwent randomization. The analysis populations are shown in Figure 1. The baseline characteristics were similar across the trial groups (Table 1).

Efficacy

Venograms that could be evaluated were obtained in 400 of the 409 patients (98%) who received trial medication (Fig. 1). In 3 of the patients whose venograms could be evaluated, venography was performed outside days 8 to 12; none of these patients had deep-vein thrombosis.

Venous thromboembolism occurred in 13 of 102 patients (13%) in the 30-mg abelacimab group, 5 of 99 patients (5%) in the 75-mg abelacimab group, and 4 of 98 patients (4%) in the 150-mg abelacimab group, as compared with 22 of 101 patients (22%) in the enoxaparin group (Table 2). All three abelacimab regimens met the criterion for noninferiority to enoxaparin. The difference in risk (abelacimab minus enoxaparin) with the 30-mg abelacimab regimen was −9.2 percentage points (95% confidence interval [CI], −19.4 to 1.1; $P=0.08$ for superiority), whereas the difference with the 75-mg abelacimab regimen was −16.8 percentage points (95% CI, −26.0 to −7.6; $P<0.001$ for superiority) and the difference with the 150-mg abelacimab regimen was −17.8 percentage points (95% CI, −26.7 to −8.8; $P<0.001$ for superiority). The per-protocol analysis yielded similar results (Table S1 in the Supplementary Appendix).

No patients had symptomatic pulmonary embolism. One patient had symptoms of deep-vein thrombosis at the time of venography. There were no deaths or cases of symptomatic venous thromboembolism after venography through day 110.

Bleeding

Clinically relevant bleeding through day 30 occurred in 2 of 102 patients (2%) in the 30-mg abelacimab group, in 2 of 104 patients (2%) in the 75-mg abelacimab group, in none of 99 patients in the 150-mg abelacimab group, and in none of 104 patients in the enoxaparin group (Table 2). The 2 patients in the 30-mg abelacimab group had clinically relevant nonmajor bleeding. One patient in the 75-mg abelacimab group had clinically relevant nonmajor bleeding; the other had clinically relevant nonmajor bleeding on day 6 and had a joint infection and hemarthrosis on day 12 that led to surgical drainage and was classified as major bleeding. The preoperative and postoperative hemoglobin levels (Fig. S2) and the frequency of blood transfusions (Table 2) were similar across the trial groups.

Other Safety Outcomes

The rates of adverse events are shown in Table 2. Serious adverse events occurred during the trial intervention in 1%, 3%, and 1% of the patients in the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, and in none of the patients in

the enoxaparin group (Table S2). None of the abelacimab infusions were stopped early because of hypersensitivity reactions, and no antidrug antibodies were detected with abelacimab infusion.

Pharmacokinetic and Pharmacodynamic Data

Abelacimab increased the activated partial-thromboplastin time ratios in a dose-dependent manner, whereas enoxaparin did not increase the ratios (Fig. 2A). Factor XI activity and free factor XI levels were inversely correlated with plasma concentrations of abelacimab (Fig. 2B, 2C, and 2D). The levels were low on day 3 with all three abelacimab regimens and remained low on day 10 with the 75-mg and 150-mg regimens but not with the 30-mg regimen.

Discussion

This trial showed that the single 30-mg dose of abelacimab was noninferior to enoxaparin for the prevention of postoperative venous thromboembolism, and the single 75-mg and 150-mg doses of abelacimab were superior to enoxaparin, with incidences of venous thromboembolism of 22% in the enoxaparin group, 13% in the 30-mg abelacimab group, 5% in the 75-mg abelacimab group, and 4% in the 150-mg abelacimab group. The rate of major or clinically relevant nonmajor bleeding was low in all the trial groups. The frequency of blood transfusions and postoperative hemoglobin levels with abelacimab were similar to those with enoxaparin. Therefore, this trial showed that the postoperative initiation of factor XI inhibition was an effective method for reducing the risk of venous thromboembolism after total knee arthroplasty and was associated with a low risk of bleeding.

Abelacimab has a unique mechanism of action. When administered intravenously, abelacimab rapidly binds to factor XI and prevents its activation by locking it in the inactive precursor conformation. By lowering the functional factor XI level, abelacimab has an effect similar to that of factor XI knockdown. This concept is supported by the observation that both abelacimab and a factor XI antisense oligonucleotide were shown to be superior to enoxaparin for the prevention of postoperative venous thromboembolism.[4] However, the antisense oligonucleotide must be administered for 4 weeks before surgery to induce knockdown of factor XI to therapeutic levels, whereas the intravenous infusion of abelacimab reduces the functional factor XI level within minutes, thereby enabling postoperative dosing.

The lower incidences of thrombosis and the less extensive thrombosis observed with the higher doses of abelacimab than with enoxaparin highlight the role of factor XI in the pathogenesis of venous thrombosis after surgery. Factor XI can be activated by factor XIIa or by thrombin and is important for thrombus growth and stabilization.[11] Abelacimab inhibits the activation of factor XI by either activator; the findings in this trial suggest that factor XI is at least as important as tissue factor in the pathogenesis of postoperative venous thromboembolism. Therefore, factor XI is an attractive target for

thromboprophylaxis. Additional studies are needed to determine the efficacy of this mechanism of factor XI inhibition for the treatment of established venous or arterial thrombosis.

Some methodologic aspects of our trial require comment. First, the strength of our conclusion regarding the low rate of bleeding observed with abelacimab is limited by the modest sample size. Therefore, further studies are needed to confirm the safety of abelacimab. Second, the trial was open-label with respect to assignment to abelacimab or enoxaparin. However, to minimize bias, the trial was blinded with respect to assignment to an abelacimab regimen, and all outcomes were adjudicated by a committee whose members were unaware of the trial-group assignments. Third, 98% of the patients had a venogram that could be evaluated for efficacy, and the small number of patients who did not have a venogram that could be evaluated were spread across the trial groups. Finally, although patient recruitment was stopped early for administrative reasons, this change did not affect the assessment of the efficacy of abelacimab.

In summary, abelacimab reduced the risk of postoperative thromboembolism to a greater extent than conventional anticoagulants such as enoxaparin, without increasing the risk of bleeding. Further studies are needed to determine whether anticoagulant strategies targeting factor XI can dissociate thrombosis from hemostasis.

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Data sharing

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Financial disclosure

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Visual Abstract

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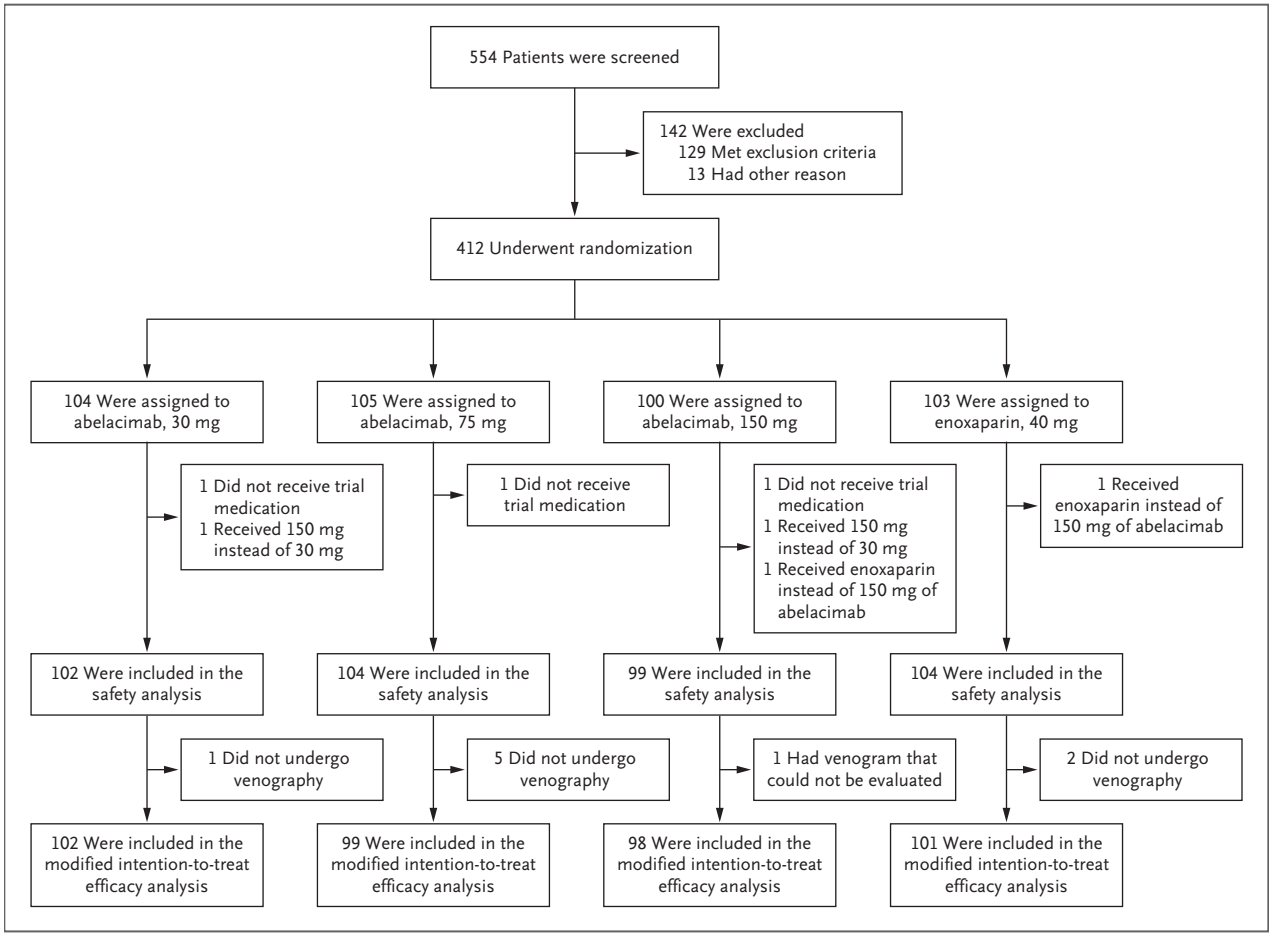

Figure 1. Enrollment, Randomization, and Populations for Analysis.

One patient who was randomly assigned to the 30-mg abelacimab group received 150 mg of abelacimab; that patient was included in the 150-mg abelacimab group for the safety analysis and in the 30-mg abelacimab group for the modified intention-to-treat efficacy analysis. One patient who was randomly assigned to the 150-mg abelacimab group received enoxaparin; that patient was included in the enoxaparin group for the safety analysis and in the 150-mg abelacimab group for the modified intention-to-treat efficacy analysis.

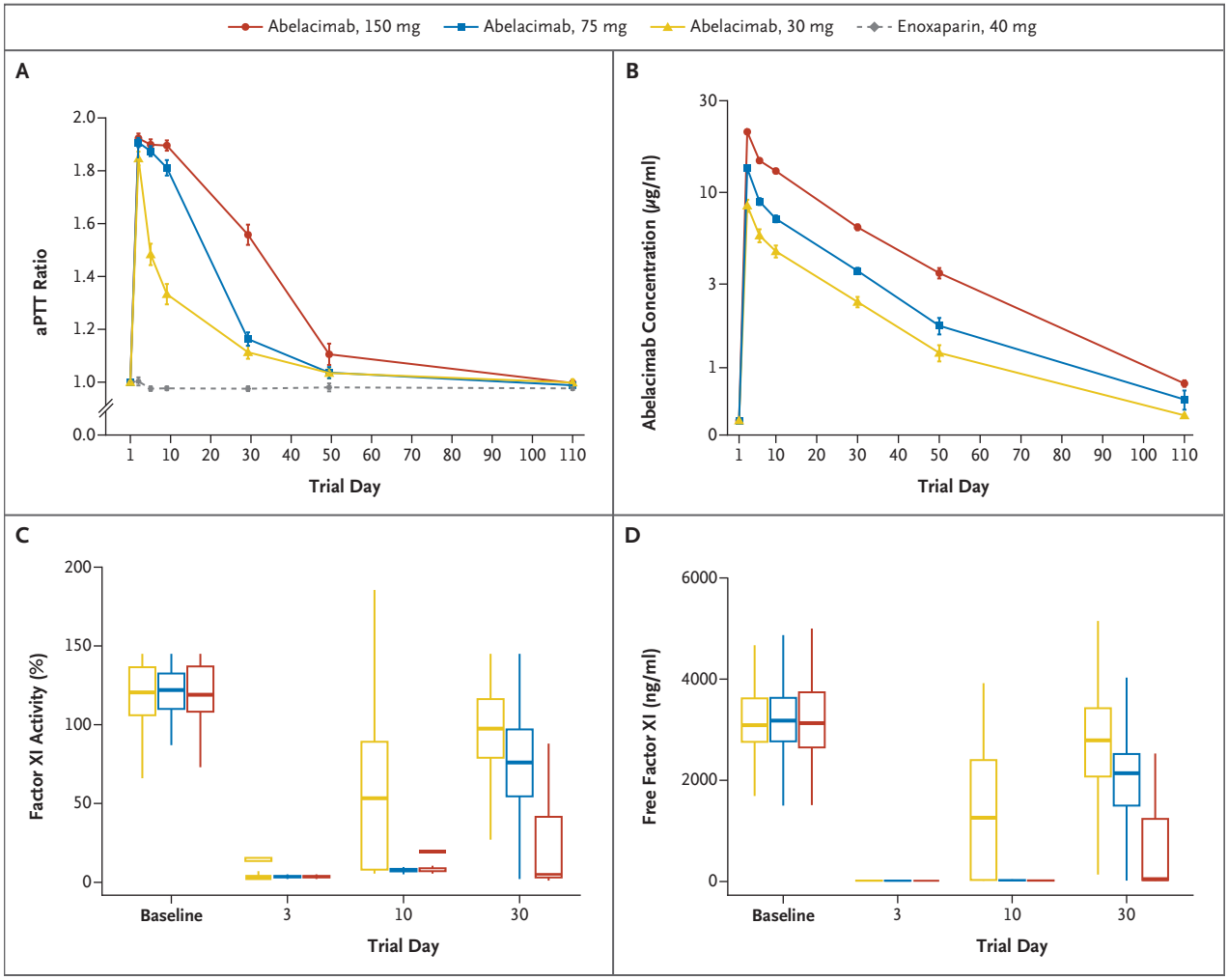

Figure 2. Activated Partial-Thromboplastin Time Ratios, Abelacimab Concentrations, Factor XI Activity, and Free Factor XI Levels.

Panel A shows mean activated partial-thromboplastin time (aPTT) ratios and Panel B mean plasma concentrations of abelacimab. For these outcomes, baseline samples were collected just before surgery on day 1. I bars indicate standard errors. Panel C shows median factor XI activity and Panel D median free factor XI levels (which indicate the concentration of factor XI without bound abelacimab). For these outcomes, baseline samples were collected during screening or just before surgery on day 1. In the plots, the middle line indicates the median; the top and bottom of the box indicate the upper and lower limits, respectively, of the interquartile range; and the vertical lines above and below the box indicate the upper and lower limits, respectively, of the range.

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

Characteristic	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Modified intention-to-treat population				
No. of patients	102	99	98	101
Age — yr				
Median	67	67	68	67
Range	49–81	41–80	49–80	45–79
Female sex — no. (%)	89 (87)	80 (81)	77 (79)	81 (80)
Weight — kg				
Median	90	86	89	94
Range	51–129	50–130	57–126	62–127
Estimated glomerular filtration rate — ml/min/1.73 m^2				
Median	78	78	77	76
Range	40–123	48–125	36–161	46–120
Type of anesthesia — no. (%)				
General	0	1 (1)	2 (2)	1 (1)
Spinal	88 (86)	90 (91)	86 (88)	88 (87)
Epidural	10 (10)	6 (6)	6 (6)	9 (9)
Duration of surgery — hr				
Median	1.3	1.3	1.3	1.3
Range	0.7–2.5	0.7–3.0	0.6–2.9	0.6–2.9
Tourniquet use — no. (%)	56 (55)	57 (58)	54 (55)	58 (57)
Duration of tourniquet use — min				
Median	53	50	50	60
Range	7–125	8–125	8–120	8–130
Time after surgery to ambulation — days				
Median	1	1	1	1
Range	0.5–5.0	0.5–1.0	0.5–2.0	0.5–2.0
Length of hospital stay — days				
Median	10	10	10	10
Range	7–15	3–18	6–17	4–16
Baseline factor XI activity — %†				
Median	118	121	117	120
Range	66–145	66–144	64–144	90–145
Baseline activated partial-thromboplastin time — sec‡				
Median	26	26	26	26
Range	22–32	21–35	22–40	20–38
Safety population				
No. of patients	102	104	99	104
Duration of enoxaparin administration — days§				
Median	NA	NA	NA	9
Range	NA	NA	NA	6–12
Time after surgery to abelacimab initiation — hr				
Median	5	5	5	NA
Range	4–7	4–7	3–8	NA

* The modified intention-to-treat population consisted of all patients who received at least one dose of trial medication and could be evaluated for the primary efficacy outcome. The safety population consisted of all patients who received at least one dose of trial medication. There were no clinically important differences among the trial groups in any of the listed characteristics. NA denotes not applicable.
† The normal range for factor XI activity is 60 to 150%.
‡ The normal range for the activated partial-thromboplastin time is 22 to 29 seconds.
§ In the enoxaparin group, 17 of 104 patients (16%) received their first dose before surgery.

Table 2. Efficacy and Safety Outcomes.*

Outcome	Abelacimab, 30 mg	Abelacimab, 75 mg	Abelacimab, 150 mg	Enoxaparin, 40 mg
Efficacy				
No. of patients evaluated	102	99	98	101
Primary efficacy outcome: venous thromboembolism†				
Any event — no. of patients (%)	13 (13)	5 (5)	4 (4)	22 (22)
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	−9.2 (−19.4 to 1.1)	−16.8 (−26.0 to −7.6)	−17.8 (−26.7 to −8.8)	NA
P value for superiority of abelacimab to enoxaparin	0.08	<0.001	<0.001	NA
Components of the primary efficacy outcome — no. (%)				
Symptomatic venous thromboembolism	0	0	0	1 (1)‡
Asymptomatic deep-vein thrombosis	13 (13)	5 (5)	4 (4)	21 (21)
Proximal deep-vein thrombosis	1 (1)	0	0	2 (2)
Distal deep-vein thrombosis	12 (12)	5 (5)	4 (4)	20 (20)‡
Extent of deep-vein thrombosis on venography — no.				
Confluent distal into proximal	1	0	0	2
Isolated proximal				
Large: ≥10 cm	0	0	0	0
Small: <10 cm	0	0	0	0
Isolated distal				
Extensive: ≥2 veins	2	0	2	8
Limited: <2 veins	10	5	2	12‡
Safety				
No. of patients evaluated	102	104§	99	104
Major or clinically relevant nonmajor bleeding				
From randomization until venography was completed				
Any event — no. of patients (%)	2 (2)	2 (2)	0	0
Risk difference, abelacimab vs. enoxaparin — percentage points (95% CI)	1.9 (−0.7 to 4.6)	1.9 (−0.7 to 4.5)	0	NA
Major bleeding — no. (%)	0	0	0	0
Clinically relevant nonmajor bleeding — no. (%)	2 (2)	2 (2)	0	0
From randomization through day 30 — no. (%)				
Any event	2 (2)	2 (2)¶	0	0
Major bleeding	0	1 (1)	0	0
Clinically relevant nonmajor bleeding	2 (2)	2 (2)	0	0
Receipt of blood transfusion through day 30 — no. (%)	6 (6)	8 (8)	9 (9)	7 (7)
Adverse events — no. of patients (%)				
Serious adverse event	1 (1)‖	3 (3)	1 (1)	0
≥1 Adverse event	15 (15)	16 (15)	15 (15)	13 (13)

* Efficacy outcomes were assessed in the modified intention-to-treat population and safety outcomes in the safety population. CI denotes confidence interval and NA not applicable.
† Venous thromboembolism is a composite of asymptomatic deep-vein thrombosis (detected by mandatory unilateral ascending venography), confirmed symptomatic venous thromboembolism (symptomatic deep-vein thrombosis of the leg or nonfatal pulmonary embolism), fatal pulmonary embolism, or unexplained death for which pulmonary embolism could not be ruled out.
‡ One patient in the enoxaparin group had calf pain on the day of venography; the venogram showed isolated distal deep-vein thrombosis.
§ Two patients in the 75-mg abelacimab group withdrew early from the trial (on day 6 and on day 30).
¶ One patient in the 75-mg abelacimab group had two bleeding events: clinically relevant nonmajor bleeding on day 6 and a joint infection and hemarthrosis on day 12 that led to surgical drainage and was classified as major bleeding.
‖ One patient in the 30-mg abelacimab group had two serious adverse events.