Efficacy of Early Prophylaxis Against Catheter-Associated Thrombosis in Critically Ill Children: A Bayesian Phase 2b Randomized Clinical Trial*

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OBJECTIVES: We obtained preliminary evidence on the efficacy of early prophylaxis on the risk of central venous catheter-associated deep venous thrombosis and its effect on thrombin generation in critically ill children.

DESIGN: Bayesian phase 2b randomized clinical trial.

SETTING: Seven PICUs.

PATIENTS: Children less than 18 years old with a newly inserted central venous catheter and at low risk of bleeding.

INTERVENTION: Enoxaparin adjusted to anti-Xa level of 0.2–0.5 international units/mL started at less than 24 hours after insertion of central venous catheter (enoxaparin arm) versus usual care without placebo (usual care arm).

MEASUREMENTS AND MAIN RESULTS: At the interim analysis, the proportion of central venous catheter-associated deep venous thrombosis on ultrasonography in the usual care arm, which was 54.2% of 24 children, was significantly higher than that previously reported. This resulted in misspecification of the preapproved Bayesian analysis, reversal of direction of treatment effect, and early termination of the randomized clinical trial. Nevertheless, with 30.4% of 23 children with central venous catheter-associated deep venous thrombosis on ultrasonography in the enoxaparin arm, risk ratio of central venous catheter-associated deep venous thrombosis was 0.55 (95% credible interval, 0.24–1.11). Including children without ultrasonography, clinically relevant central venous catheter-associated deep venous thrombosis developed in one of 27 children (3.7%) in the enoxaparin arm and seven of 24 (29.2%) in the usual care arm ($p = 0.02$). Clinically relevant bleeding developed in one child randomized to the enoxaparin arm. Response profile of endogenous thrombin potential, a measure of thrombin generation, was not statistically different between trial arms.

CONCLUSIONS: These findings suggest the efficacy and safety of early prophylaxis that should be validated in a pivotal randomized clinical trial.

KEY WORDS: Bayesian statistics; bleeding; central venous catheter; deep venous thrombosis; enoxaparin; pediatric intensive care unit

Venous thromboembolism (VTE) significantly affects the health of children (1, 2). The annual rate of VTE in hospitalized children increased by 70% over nearly a decade (3). Pediatric VTE, which is predominantly deep venous thrombosis (DVT), is the second largest contributor to harm accounting for 16% of all serious safety events in hospitalized children (4). Critical illness and central venous catheters (CVCs) are the most important

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risk factors for DVT in children (5). A meta-analysis of 676 children showed that the absolute risk of CVC-associated DVT (CADVT) diagnosed using systematic radiologic screening in critically ill children with untunneled CVC was 0.18 (95% CI, 0.12–0.25) (6).

Pediatric VTE is potentially preventable (7, 8). However, pharmacologic prophylaxis against CADVT is not recommended in hospitalized children because of paucity of pediatric randomized clinical trials (RCTs) (9). Prophylaxis of Thromboembolism in Kids Trial (PROTEKT), the largest RCT of prophylaxis against CADVT in hospitalized children, was stopped early for poor enrollment (10). In PROTEKT, risk ratio of radiologically confirmed CADVT with reviparin versus placebo was 1.2 (95% CI, 0.4–3.2). Reviparin was started late at a mean of 2.6 days after insertion of CVC when nearly 50% of CADVT would have already developed and only achieved a mean anti-Xa level of 0.1 international units (IU)/mL (10, 11). In preparation for a pivotal RCT of pharmacologic prophylaxis against CADVT, our first aim was to obtain preliminary evidence on the efficacy of early prophylaxis started within 24 hours after insertion of the CVC on the risk of CADVT in critically ill children. Our second aim was to evaluate the effect of a prophylactic strategy that targeted the typically used anti-Xa level of 0.2–0.5 IU/mL on thrombin generation, the key event in thrombus formation, in critically ill children.

MATERIALS AND METHODS

Study Design and Oversight

The Catheter-Related Early Thromboprophylaxis with Enoxaparin (CRETE) Trial was an open-label blinded endpoint Bayesian phase 2b RCT conducted in seven PICUs in the United States from November 2017 to August 2019. Children were randomized 1:1 to enoxaparin or usual care with permuted block design and variable block sizes. Computerized randomization was stratified by ICU and age, that is, less than 1, 1–13, and greater than 13 years (12). Yale Human Investigations Committee (HIC#1302011506) and local institutional review boards approved the CRETE Trial. Food and Drug Administration (FDA) approved the use of enoxaparin. Parental permission and assent, as appropriate, were obtained on enrollment. A data and safety monitoring board (DSMB) and safety monitor oversaw the CRETE Trial and reviewed the data.

Subjects

We enrolled children admitted to the ICU who were less than 24 hours after insertion of an untunneled CVC in the internal jugular or femoral vein, with CVC required for greater than or equal to 24 hours, greater than 36 weeks corrected gestational age to less than 18 years old, and with anticipated stay in the ICU greater than or equal to 48 hours. Ultrasonography is inaccurate in diagnosing subclavian CADVT (13). We excluded those with coagulopathy, clinically relevant bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH), less than 60 days from a clinically relevant bleed, less than 7 days after trauma or surgery, on concurrent antithrombotic agent, DVT at the site of insertion of the CVC in prior 6 weeks, allergy to heparin, or history of heparin-induced thrombocytopenia (HIT) (14–17). Coagulopathy was defined as international normalized ratio greater than 2.0, activated partial thromboplastin time greater than 50 seconds, or platelet count less than 50,000/mm^3 (16).

Procedures

Children randomized to enoxaparin received enoxaparin subcutaneously every 12 hours at 0.75 mg/kg for children less than or equal to 2 months old or 0.5 mg/kg (maximum of 30 mg) for others, which was adjusted for obesity and renal insufficiency (9). First dose was administered less than 24 hours after insertion of CVC and adjusted to achieve an anti-Xa level of 0.2–0.5 IU/mL. Anti-Xa level was measured locally 4–6 hours after every third dose until target was reached, then weekly. Enoxaparin continued until end of study, which was removal of CVC, or earlier upon discharge from ICU, radiologic diagnosis of CADVT, start of therapeutic anticoagulation, or 28 days after insertion of CVC. Enoxaparin was discontinued after a clinically relevant bleed, and held 12 hours before surgery or invasive procedure, for new coagulopathy, or suspected HIT. Enoxaparin was resumed 24 hours after coagulopathy was corrected, 24 hours after surgery or procedure, and after HIT was excluded. Children randomized to usual care did not receive placebo. Ultrasonography of the vein proximal and distal to site of insertion of the CVC was performed by blinded technicians using standard procedures within 24 hours of end of study (13). Children were monitored daily for bleeding (18).

Blood was drawn into citrated tubes (BD Vacutainer Plus Plastic Citrate Tubes, Becton and Dickinson Company, Franklin Lakes, NJ) on the day of, day after, and day 4 after insertion of CVC, processed locally for platelet poor plasma, and then frozen at –70°C until analyzed. Endogenous thrombin potential (ETP), a measure of thrombin generation, was measured from plasma using Calibrated Automated Thrombogram (Thrombinoscope, Maastricht, the Netherlands) and 1 pM of tissue factor (PPP-Reagent LOW, Stago Diagnsotica, Parsippany, NJ) per manufacturer's protocol. Factor VIII activity and D-dimer level were measured using Siemens Factor VIII Chromogenic Assay and Stratus CS Acute Care DDMR Testpak (Siemens Healthcare Diagnostics, Newark, DE), respectively.

Outcome Measures

The primary outcome for the first aim was the presence of CADVT, defined as DVT in the site of insertion of the CVC confirmed by ultrasonography. A committee of three pediatric radiologists blindly and independently diagnosed CADVT (13). CADVT was diagnosed if greater than two were present: IV echogenic material adherent to the venous wall, noncompressibility of the vein, or abnormal venous Doppler (19). At least two concurring radiologists were needed to diagnose CADVT. Their diagnosis was not relayed to the clinical team. However, a local radiologist read the images and provided results to the clinical team who decided on treatment. Complete or partial occlusion of flow defined an occlusive or nonocclusive CADVT, respectively (20). Clinically relevant CADVT was defined as a radiologically diagnosed CADVT that had signs of DVT, including dysfunction of the CVC, as detected by the clinical team, or that was treated by the clinical team (21, 22). Secondary outcomes included measures of efficacy, safety, feasibility, and compliance. The primary outcome for the second aim was ETP with factor VIII activity and D-dimer level as secondary outcomes.

Statistical Considerations

The CRETE Trial was designed and approved by the FDA and DSMB to use Bayesian inference for primary analysis of the first aim. Statistical details are in the **Supplemental Material** (http://links.lww.com/CCM/G42). Bayesian inference proceeds by weighted averaging of previous information, that is, prior, and likelihood function of observed data to produce updated information, that is, posterior (23). In the presence of pertinent information, informative priors can be used. In its absence, minimally informative priors are used. Borrowing of information with informative priors can mitigate the effect of limited sample size (24). Estimates of parameters of interest, for example, risk of CADVT and risk ratio with enoxaparin, are reported from the posteriors.

We planned to enroll 100 children. For the primary analysis comparing the risk of CADVT between the trial arms, risk of CADVT without prophylaxis from the meta-analysis was used as informative prior for the usual care arm (**Supplemental figure**, http://links.lww.com/CCM/G43; **legend**, http://links.lww.com/CCM/G42) (6). Minimally informative prior was used for the enoxaparin arm, because information was not available. We planned to test the absolute difference in the risks of CADVT to leverage the available information. Our statistical hypothesis was that there was greater than 60% probability that the difference in the risk of CADVT was greater than or equal to 0.06 points, in terms of risk, lower with prophylaxis. This represented a clinically significant relative risk reduction with enoxaparin of greater than or equal to 33%, assuming the risk of CADVT without prophylaxis was 0.18 (6). In the supportive analysis, we chose an approach that was free of assumptions on the risks of CADVT and estimated the risk ratio of CADVT with enoxaparin using minimally informative prior given the absence of pertinent information on treatment effect. The risks and ratio were reported as medians of the posteriors with 95% equal-tailed credible intervals (CrIs). FDA requested an interim efficacy analysis after 50 children were randomized. Data from these children were used to determine the probability of proving our hypothesis using predictive probability (25). The CRETE Trial would be terminated for futility if this predictive probability was less than 10%.

Frequentist analyses were performed for comparison and in the absence of prespecified analysis for the second aim and secondary outcome measures (26). Chi-squared or Fisher exact tests were used to compare categorical variables between the trial arms, whereas Mann-Whitney *U* test was used to compare continuous variables. Linear mixed-effects model

that included the interaction between trial arm and sampling day regarded as a categorical variable assessed the associations of ETP, factor VIII activity, and D-dimer level with treatment with random intercept per child. Statistical test of the null hypothesis of no interaction compared mean response profiles, defined as patterns of change in biomarker level from the day of insertion of the CVC, between the trial arms (27). A p value of less than 0.05 was considered statistically significant.

Data were presented as counts (%) or median (interquartile range [IQR]). Intention to treat principle was applied to all analyses. All statistical analyses were conducted using Stata 16.1 (StataCorp, College Station, TX).

RESULTS

Subjects

The DSMB recommended termination after interim analysis. The predictive probability was 0.9% (Supplemental Material, http://links.lww.com/CCM/G42).

A total of 51 of 164 eligible children (31.1%) were randomized to enoxaparin (n = 27) or usual care (n = 24) (**Fig. 1**). Median age was 2.8 years (IQR, 0.4–8.9 yr) in the enoxaparin arm and 1.0 years (IQR, 0.3–8.9 yr) in the usual care arm (**Table 1**). CVC was most commonly inserted in the right internal jugular vein in the enoxaparin (55.6%) and usual care (54.2%) arms. Co-interventions were comparable, except for use of neuromuscular blockade, which was more common in the enoxaparin arm (77.8% vs 37.5% in the usual care arm). None received additional anticoagulants or aspirin. Use of mechanical thromboprophylaxis was comparable.

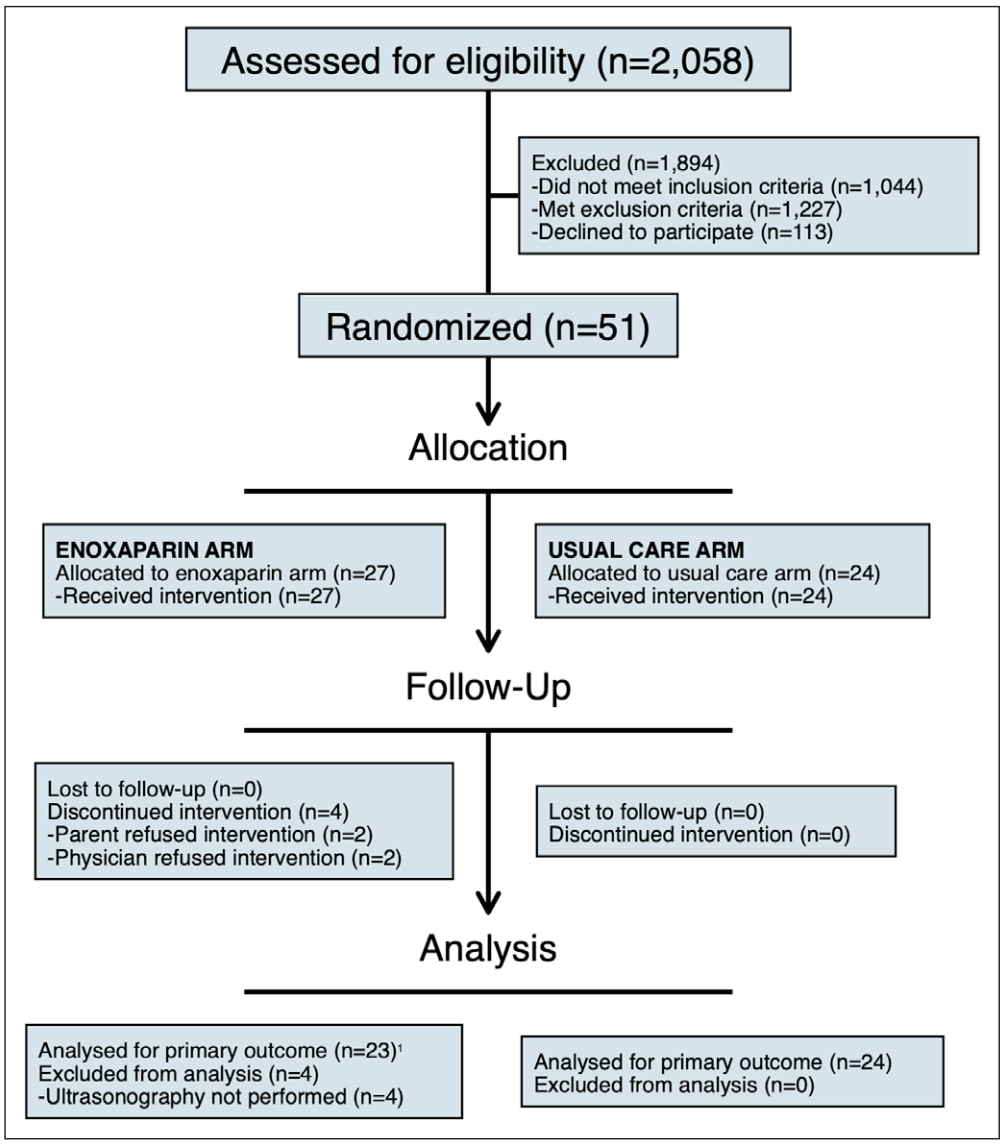

Figure 1. CONSORT diagram. [1]All children, regardless of the presence of ultrasonography, were analyzed for the other outcome measures.

Efficacy of Early Prophylaxis on CADVT

All children randomized to enoxaparin received the drug (median, 6 doses; IQR, 3–13 doses). Of 272 scheduled doses, 8 (2.9%) were not given. The first dose was administered at a median of 21.1 hours (IQR, 14.7–23.5 hr) after the insertion of CVC. Of 21 children with at least one anti-Xa level, target was achieved in 12 children (57.1%) at a median of 70.4 hours (IQR, 47.4–93.2 hr) after the insertion of CVC (**Supplemental Table 1**, http://links.lww.com/CCM/G44). The remaining children completed the study before

TABLE 1.
Baseline Characteristics and Cointerventions of Children in the Enoxaparin and Usual Care Arms

Variable	Enoxaparin Arm (*n* = 27)	Usual Care Arm (*n* = 24)	*p*
Baseline characteristics			
Age category			
< 1 yr old	12 (44.4)	12 (50.0)	0.91
1–13 yr old	13 (48.1)	10 (41.7)	
> 13 yr old	2 (7.4)	2 (8.3)	
Female sex	16 (59.3)	12 (50.0)	0.51
Weight (kg)	10.4 (6.5–23.5)	9.3 (6.1–26.5)	0.79
Pediatric Index of Mortality 2	0.03 (0–0.2)	0.03 (0–0.1)	0.42
Race and ethnicity			
Non-Hispanic White	17 (63.0)	14 (58.3)	0.96
Non-Hispanic Black	4 (14.8)	5 (20.8)	
Non-Hispanic mixed	1 (3.7)	0 (0)	
Hispanic	5 (18.5)	5 (20.8)	
Presence of cancer	1 (3.7)	0 (0)	1.00
Presence of systemic infection	15 (55.6)	15 (62.5)	0.62
Presence of congenital heart disease	2 (7.4)	2 (8.3)	1.00
Presence of permanent immobility	3 (11.1)	2 (8.3)	1.00
Presence of recent surgery	0 (0)	2 (8.3)	0.22
Personal history of venous thromboembolism	1 (3.7)	0 (0)	1.00
Size of central venous catheter			
3F	0 (0)	2 (8.3)	0.35
4F	13 (48.1)	11 (45.8)	
5F	10 (37)	10 (41.7)	
7F	4 (14.8)	1 (4.2)	
Number of lumens of central venous catheter			
1	0 (0)	2 (8.3)	0.50
2	15 (55.6)	12 (50.0)	
3	12 (44.4)	10 (41.7)	

(*Continued*)

TABLE 1. (*Continued*)
Baseline Characteristics and Cointerventions of Children in the Enoxaparin and Usual Care Arms

Variable	Enoxaparin Arm (*n* = 27)	Usual Care Arm (*n* = 24)	*p*
Site of insertion of central venous catheter			
Left femoral	4 (14.8)	4 (16.7)	1.00
Right internal jugular	15 (55.6)	13 (54.2)	
Right femoral	8 (29.6)	7 (29.2)	
Platelet count (× 10^3/mm^3)	281 (191–315)	250 (172–310)	0.37
Hemoglobin (g/dL)	9.7 (9.1–11.3)	9.9 (8.9–11.5)	0.81
International normalized ratio	1.2 (1.0–1.4)	1.2 (1.1–1.4)	0.37
Activated partial thromboplastin time (s)	33.4 (28.7–38.5)	32.1 (29.3–37.0)	0.52
Cointerventions			
Vasopressor	14 (51.9)	12 (50.0)	0.90
Noninvasive ventilation	7 (25.9)	6 (25.0)	0.94
Mechanical ventilation	26 (96.3)	21 (87.5)	0.33
Neuromuscular blockade	21 (77.8)	9 (37.5)	0.004
IV unfractionated heparin	18 (66.7)	18 (75.0)	0.51
Subcutaneous unfractionated heparin	0 (0)	0 (0)	–
Low-molecular-weight heparin	0 (0)	0 (0)	–
Aspirin	0 (0)	0 (0)	–
Vitamin K antagonist	0 (0)	0 (0)	–
Mechanical thromboprophylaxis	2 (7.4)	2 (8.3)	1.00
Platelet transfusion	1 (3.7)	1 (4.2)	1.00
RBC transfusion	5 (18.5)	4 (16.7)	1.00
Plasma transfusion	1 (3.7)	1 (4.2)	1.00
Parenteral nutrition	4 (14.8)	5 (20.8)	0.72

Data are presented as count (%) or median (interquartile range)—not estimable.

achieving target (**Supplemental Table 2**, http://links.lww.com/CCM/G45). Anti-Xa level was within target in six children (28.6%) when first measured.

Ultrasonography was performed in 47 children (92.2%). Of four who did not have ultrasonography, three had impending death and one was withdrawn after enrollment when the CRETE Trial was terminated. A total of seven of 23 children (30.4%) with ultrasonography in the enoxaparin arm and 13 of 24 children (54.2%) in the usual care arm had CADVT (p = 0.10) (**Table 2**). The posterior risks of CADVT were 0.34 (95% Crl, 0.18–0.54) in the enoxaparin arm and 0.24 (95% CrI, 0.17–0.32) in the usual care arm. Posterior risk ratio of CADVT with enoxaparin was 0.55 (95% CrI, 0.24–1.11) (**Fig. 2**). All CADVTs in the enoxaparin arm were nonocclusive. In the usual care

TABLE 2.
Comparison of Efficacy and Safety Outcomes Between Enoxaparin and Usual Care Arms

Variable	Enoxaparin Arm ($n = 27$)	Usual Care Arm ($n = 24$)	p
Efficacy outcome measures			
Central venous catheter-associated deep venous thrombosis[a]	7 (30.4)	13 (54.2)2	0.10
Other thromboembolic event	1 (3.7)	1 (4.2)	1.00
PICU length of stay	12 (6–22)	8 (4–16)	0.31
Hospital length of stay	16 (6–35)	16 (7–23)	0.58
Safety outcome measures			
Any bleed	4 (14.8)	2 (8.3)	0.67
Clinically relevant bleed	1 (3.7)	0 (0)	1.00
Heparin-induced thrombocytopenia	0 (0)	0 (0)	–
Death	5 (18.5)	2 (8.3)	0.43

[a]Only 23 children in the enoxaparin arm had ultrasonography.
Data are presented as count (%)—not estimable.

arm, 11 were nonocclusive and two were occlusive ($p = 0.15$). Clinically relevant CADVT developed in one of 27 children (3.7%) in the enoxaparin arm and seven of 24 children (29.2%) in the usual care arm ($p = 0.02$). Of children who did not have ultrasonography, none had signs of CADVT. Other outcome measures were not statistically different between trial arms (Table 2).

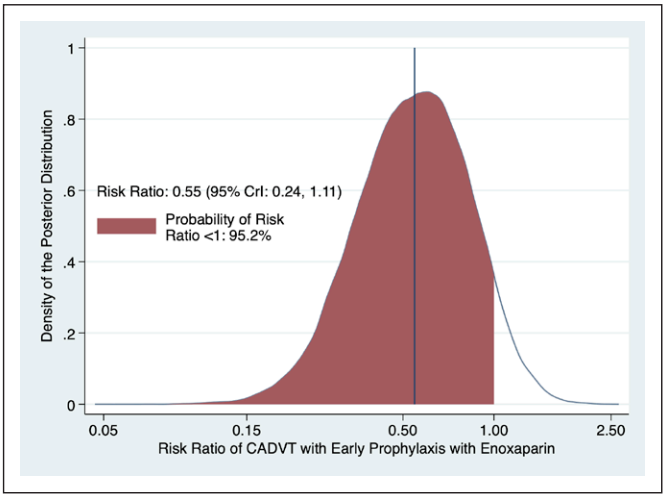

Figure 2. Posterior distribution of the risk ratio of central venous catheter-associated deep venous thrombosis (CADVT) with early prophylaxis with enoxaparin. The *vertical line* represents the posterior median of the probability distribution of the risk ratio, whereas the *shaded area* represents the posterior probability that the risk ratio is < 1. CrI = credible interval.

A total of four (14.8%) children in the enoxaparin arm bled with one (3.7%) clinically relevant bleed in the upper airway that required platelet transfusion (Table 2). In the usual care arm, two children (8.3%) bled, none of which were clinically relevant ($p = 1.00$). A total of five children (18.5%) in the enoxaparin arm and two (8.3%) in the usual care arm died ($p = 0.43$). The deaths were unrelated to enoxaparin.

Effect of Anti-Xa Level-Directed Prophylactic Strategy on Thrombin Generation

ETP on the day of insertion of the CVC was not statistically different between enoxaparin (median, 919.70 nM.min; IQR, 418.71–1150.77 nM.min) and usual care (median, 1,035.60 nM.min; IQR, 800.22–1,455.05 nM.min; $p = 0.22$) arms (**Fig. 3**). Response profiles of ETP, factor VIII activity, and D-dimer level were not statistically different between the trial arms (Fig. 3; and **Supplemental Table 3**, http://links.lww.com/CCM/G46).

DISCUSSION

The CRETE Trial was designed to obtain preliminary evidence on the efficacy of early prophylaxis against CADVT in critically ill children. It was terminated early

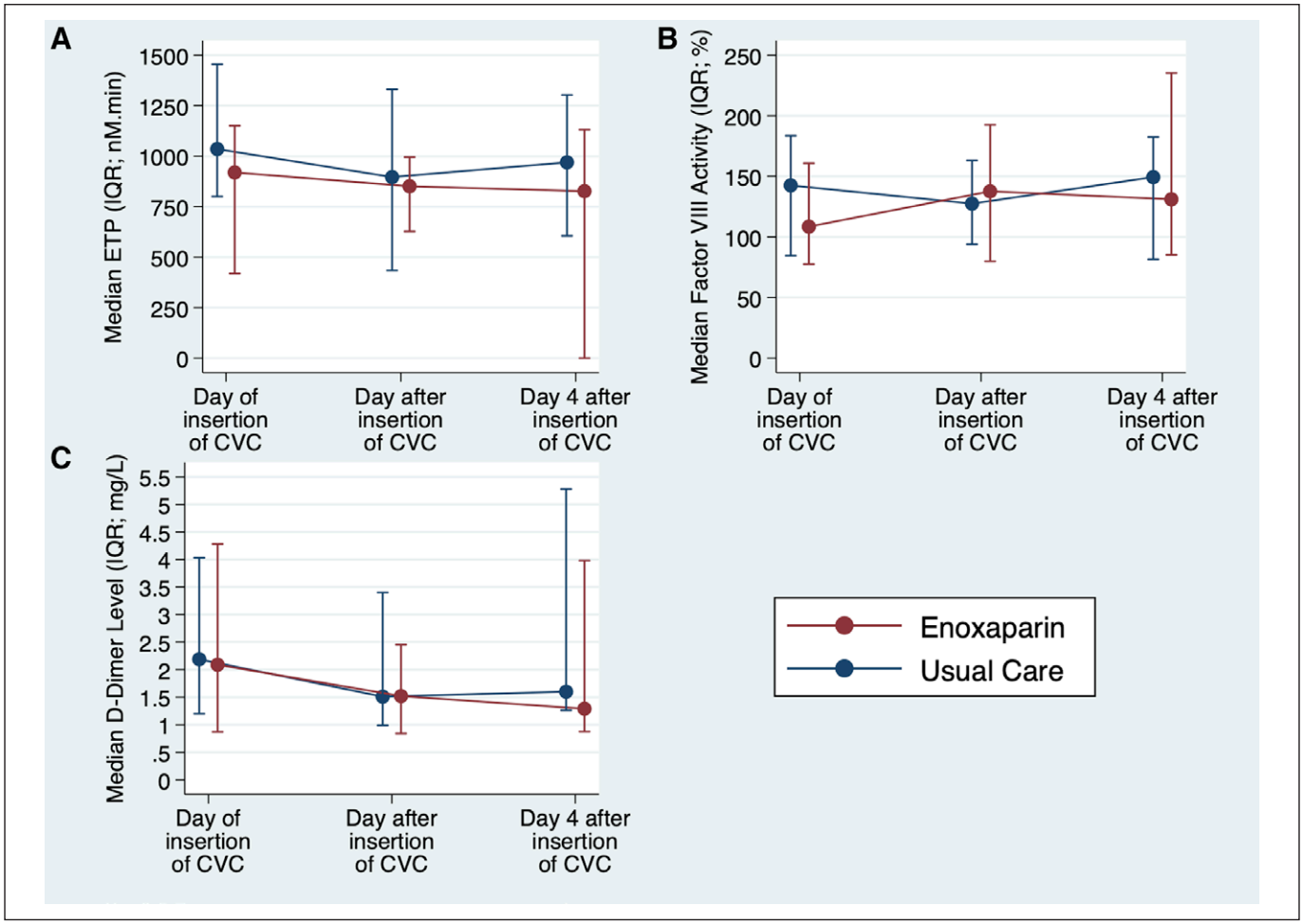

Figure 3. Levels of biomarkers. Response profiles of (**A**) endogenous thrombin potential (ETP), (**B**) factor VIII activity, and (**C**) D-dimer level across sampling days and between trial arms. None of the response profiles were statistically different between trial arms. CVC = central venous catheter, IQR = interquartile range.

based on misspecification in the preapproved Bayesian analysis. Nevertheless, the risk ratio of CADVT with enoxaparin was 0.55 (95% CrI, 0.24–1.11) in the interim analysis. The risk of clinically relevant bleeding was not statistically different with enoxaparin. We did not observe a reduction in ETP with the anti-Xa level-directed strategy. Although the CRETE Trial was terminated early for futility and the CrI of treatment effect with half the total sample size was wide and included no effect, our findings support the conduct and inform the design of a future pivotal RCT.

Bayesian inference is sensitive to choice of prior (28). We based our prior on the strong information about the risk of CADVT without prophylaxis from multiple studies (6). Unfortunately, our study population likely were sicker on enrollment with the proportion of children in the usual care arm who developed CADVT being three-fold higher than previously reported (6, 29). In the Bayesian analysis, the strong prior risk of 0.18 with little variability shrunk the observed information from the proportion of CADVT in the usual care arm of 0.54 to the posterior risk of 0.24. The observed proportion of CADVT in the usual care arm was higher, but the posterior risk was lower than the posterior risk of CADVT in the enoxaparin arm of 0.34. Shrinkage did not occur in the enoxaparin arm, because its prior was minimally informative with large variability. Due to the misspecified prior about the risk of CADVT, the direction in estimated treatment effect was reversed. Consequently, the predictive probability met the criteria for termination. Given the preapproved statistical approach and unusually high proportion of children with CADVT, continuing the CRETE Trial would be futile and unable to prove that the posterior risk of CADVT with enoxaparin was greater than or equal to 0.06 points lower than that without

enoxaparin. The supportive analysis using minimally informative priors on the risk ratio of CADVT with enoxaparin resolved the misspecification and provided analyses that were consistent with the observed data and analogous frequentist analyses. We plan to use the risk ratio of CADVT from the CRETE Trial to design a future pivotal RCT. This risk ratio does not depend on the risks of CADVT and will avoid misspecification.

The potential efficacy of early prophylaxis was supported by proportionately less clinically relevant CADVT and less severe venous occlusion with enoxaparin. These findings are consistent with the natural history of CADVT in critically ill children. In these children, the risk of CADVT is less than 2.5% within 24 hours after insertion of an untunneled CVC (19). Starting pharmacologic prophylaxis when the risk of CADVT is low likely increased its efficacy. In children with acute leukemia, enoxaparin appeared to reduce the risk of thromboembolism when started prior to asparaginase (30). Delayed administration of reviparin in the PROTEKT Trial likely contributed to its negative findings (10). The risk of clinically relevant bleeding in the CRETE Trial was consistent with published reports (31, 32).

Thrombin generation, for example, as measured by ETP, is the pharmacodynamic target of pharmacologic prophylaxis against CADVT. Anti-Xa level is a pharmacokinetic parameter and has moderate correlation with ETP (33, 34). We hypothesized that an anti-Xa-targeted strategy of prophylaxis with enoxaparin would reduce ETP and D-dimer level, an indirect measure of thrombin generation, but not factor VIII activity, a procoagulant unaffected by enoxaparin (35–37). Enoxaparin did not alter the response profiles of ETP, factor VIII activity, or D-dimer level, likely due to the lack of statistical power, particularly because the CRETE Trial was terminated early. We achieved target anti-Xa level in only 51.4% of children and at nearly day 4 after insertion of the CVC when most CADVT would have already developed (19). A higher dose of enoxaparin that will result in lower ETP and shorter time to reach target anti-Xa level should be investigated given the high proportion of CADVT in our enoxaparin arm at 30.4% (38). Lower dose comparable with that in adults may also not be inferior to the dose we used and achieve the same efficacy against CADVT (39). Other mechanisms that promote thrombus formation, for example, platelet, contact, and complement activation, should be studied, because enoxaparin may be preventing CADVT through other mechanisms (40).

The CRETE Trial has limitations. We used systematic screening with ultrasonography to define CADVT. Although ISTH recommended this definition and FDA use this to approve enoxaparin, debate is ongoing about the clinical relevance of DVT in children that has been identified by ultrasonography alone (17, 41, 42). We showed a reduction in risk of clinically relevant CADVT, but this may be biased as our design was open-label and our definition, like others', depended on practitioners' behavior (21, 22). Lack of ultrasonography may affect the magnitude of treatment effect, including on clinically relevant CADVT. Although those who did not have ultrasonography did not have signs of CADVT, it is possible, though unlikely, that they had CADVT on ultrasonography or that CADVT would be treated given their clinical status (19). Significance of our findings on long-term outcomes, such as postthrombotic syndrome, is unclear, as children were not followed after discharge (20). Risk of bleeding with enoxaparin may have been higher if those at high risk of bleeding were not excluded (32).

CONCLUSIONS

In conclusion, early prophylaxis with enoxaparin may safely reduce the risk of CADVT in critically ill children. Extreme caution should be exercised when attempting to use our findings to support clinical practice. The CrI of treatment effect was wide and included no effect. However, our preliminary evidence on the efficacy and safety of early prophylaxis against CADVT supports the conduct of a future pivotal RCT.

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APPENDIX

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