Rivaroxaban reversal with prothrombin complex concentrate or tranexamic acid in healthy volunteers

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Essentials
- Specific reversal agents for managing severe factor Xa inhibitor-associated bleeding are lacking.
- We assessed 4-factor-prothrombin complex concentrate (4F-PCC) and tranexamic acid (TXA).
- 4F-PCC, but not TXA, reduced the prothrombin time and increased endogenous thrombin potential.
- These agents may be viable options for reversal of therapeutic doses of rivaroxaban.

Summary. Background: Oral activated factor X inhibitors such as rivaroxaban are widely used, but specific reversal agents are lacking. Although four-factor prothrombin complex concentrate (4F-PCC) and tranexamic acid (TXA) are sometimes used to manage serious bleeding, their efficacy is unknown. Prior studies in healthy subjects taking rivaroxaban revealed that 4F-PCC partially reverses the prolonged prothrombin time (PT), and fully restores the endogenous thrombin potential (ETP). The effect of TXA has not been evaluated. Methods: In this double-blind, parallel-group study, 147 healthy volunteers given rivaroxaban 20 mg twice daily for 3 days were randomized after their morning dose on day 4 to receive intravenous 4F-PCC (50 IU kg⁻¹), TXA (1.0 g), or saline. Standardized punch biopsies were performed at baseline and after 4F-PCC, TXA or saline administration. Reversal was assessed by measuring bleeding duration and bleeding volume at biopsy sites, and by determining the PT and ETP. Results: As compared with saline, 4F-PCC partially reversed the PT and completely reversed the ETP, whereas TXA had no effect. Neither 4F-PCC nor TXA reduced bleeding duration or volume. All treatments were well tolerated, with no recorded adverse events. Conclusions: Although 4F-PCC reduced the PT and increased the ETP in volunteers given supratherapeutic doses of rivaroxaban, neither 4F-PCC nor TXA influenced punch biopsy bleeding.

Keywords: anticoagulants; antidotes; hemorrhage; prothrombin complex concentrate; rivaroxaban; tranexamic acid.

Introduction
Oral activated factor X (FXa) inhibitors such as rivaroxaban are replacing vitamin K antagonists (VKAs) such as warfarin for many indications. Rivaroxaban is at least as effective as VKAs for stroke prevention in atrial fibrillation and for the treatment of venous thromboembolism, but is associated with less bleeding, particularly less intracranial hemorrhage [1–3]. Nonetheless, life-threatening bleeding can occur in patients taking rivaroxaban, and management of these events represents an unmet medical need. Specific reversal agents such asandexanet alfa are not yet licensed for rivaroxaban reversal [4]. Instead, four-factor prothrombin complex concentrate (4F-PCC) and tranexamic acid (TXA) have been suggested for this purpose, and are included in guidance documents for the management of bleeding [5,6].

Recent studies in healthy volunteers have assessed the utility of both three-factor prothrombin complex concentrate and 4F-PCC for reversing the anticoagulant effects of rivaroxaban [7,8]. The results from these studies demonstrated partial to complete reversal of rivaroxaban’s effects on the prothrombin time (PT) and
endogenous thrombin potential (ETP), providing initial support for the potential utility of prothrombin complex concentrates for rivaroxaban reversal. The use of TXA, an antifibrinolytic agent, has also been suggested in patients with rivaroxaban-associated bleeding [9,10]. Although its efficacy in this setting is unknown, TXA is well tolerated and has been shown to reduce blood loss in patients undergoing surgery and in those with trauma [11]. Therefore, both 4F-PCC and TXA may be useful for rivaroxaban reversal.

To examine their potential utility for rivaroxaban reversal, 4F-PCC and TXA were administered to healthy volunteers pretreated with supratherapeutic doses of rivaroxaban (20 mg twice daily), and their effects on bleeding from standardized punch biopsies and on the PT, ETP and levels of prothrombin fragment 1 + 2 (F1 + 2) and D-dimer were determined.

Materials and methods

Study design and oversight

We performed a two-part, single-center (Quintiles Phase I Unit, Overland Park, KS, USA), phase 1, pharmacodynamic (PD) study (ClinicalTrials.gov number, NCT02561923) in healthy volunteers. Part 1 was an open-label pilot study to standardize the punch biopsy procedure and determine the relative sensitivity and variability of bleeding duration (BD) and bleeding volume (BV) in volunteers (n = 12) given a single oral 20-mg dose of rivaroxaban (Fig. S1). Part 2 was a double-blind, parallel-group study in 147 healthy volunteers given rivaroxaban 20 mg twice daily for 3 days. Before dosing, standardized punch biopsies were performed (baseline). After the final rivaroxaban dose on the morning of day 4, subjects were randomized to receive intravenous 4F-PCC (50 IU kg⁻¹), TXA (1.0 g), or saline control. Subjects were randomly assigned to one of the three treatment groups on the basis of a computer-generated randomization schedule (balanced by the use of randomly permuted blocks) prepared on day 1 predose. Blinded treatment was used to reduce potential bias during data collection and clinical endpoint evaluation. To maintain blinding, the investigator was provided with a sealed randomization code for each subject that contained coded details of the treatment in the double-blind phase. All randomization codes, whether opened or sealed, were collected at the end of the subjects’ participation. To ensure that the administration of 4F-PCC, TXA or saline control was double-blinded, a designated pharmacist at the clinical site remained unblinded and performed the preparation for all study drug administration. Opaque covers were placed over the intravenous bags and drip chamber to maintain proper blinding during treatment. Standardized punch biopsies were repeated after intravenous administration of 4F-PCC, TXA, or saline control (Fig. 1A). A 20-mg rivaroxaban dose was chosen for Part 1 because this is the usual treatment dose and because, owing to rivaroxaban’s dose-linear pharmacokinetics, higher or lower doses should not affect the sensitivity or variability of the punch biopsy variables. A 20-mg twice-daily dose was chosen for Part 2 to better mimic reversal in situations where drug levels might be elevated, such as in elderly patients with renal impairment. The 20-mg twice-daily dose also covers the exposures expected with the 15-mg twice-daily dose used for the initial treatment of venous thromboembolism. Finally, the time of 4F-PCC, TXA or saline control administration corresponded to the typical time of maximum rivaroxaban concentration in the plasma, i.e. approximately 2–4 h postdose. The study protocol was approved by the Midlands Independent Review Board (Overland Park) and was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and in accordance with the guidelines for Good Clinical Practice. All participants provided written informed consent. J. H. Levy had full access to all study data and takes responsibility for its integrity and the data analysis.

Subjects

Healthy men or healthy women of non-childbearing potential were eligible for inclusion if they were aged 18–55 years, had a body mass index (BMI) of 18–30 kg m⁻² and a body weight of 50–100 kg, had normal renal function, and had a normal PT and activated partial thromboplastin time (APTT). Subjects were ineligible if they had any known serious medical illness, bleeding or clotting disorder, poor venous access, known intracranial or intra-abdominal tumor or aneurysm, or gastrointestinal disease that could impair study drug absorption, or were taking combined P-glycoprotein and strong cytochrome P450 3A4/5 inhibitors or inducers.

Randomization

For Part 2 of the study, subjects were sequentially randomized into three cohorts in a blinded fashion: subjects in group A received 4F-PCC and TXA saline control, those in group B received 4F-PCC saline control and TXA, and those in group C received 4F-PCC saline control and TXA saline control. All three cohorts received rivaroxaban (Fig. 1B).

Study protocol

A punch biopsy was conducted on day 1 (baseline) after admission into the Phase I Unit. Rivaroxaban was given at a dose of 20 mg every 12 h within 30 min after starting a standardized meal consisting of similar content and total calorie count on days 1–3 to achieve steady-state
plasma concentrations, and a single final 20-mg dose was given on the morning of day 4. After rivaroxaban administration on day 4, subjects were given either 50 IU kg\(^{-1}\) 4F-PCC at a maximum rate of 210 IU min\(^{-1}\), 1.0 g of TXA over a period of 10 min, or saline control—all via intravenous administration, in a blinded fashion, with opaque covers over the intravenous bags and drip chambers. Infusion times were calculated such that the end of infusion of the blinded 4F-PCC (or saline control) treatment occurred 3 h and 45 min after the final rivaroxaban dose, and the end of infusion of the blinded TXA (or saline control) treatment occurred 15 min later, i.e. 4 h after the final rivaroxaban dose. A second punch biopsy was performed on day 4 after administration of 4F-PCC (or saline control) or TXA (or saline control) and no earlier than 4 h (and no later than 4 h and 15 min) after the

Fig. 1. Overview of Part 2 study. Study design (A) and schematic of blinded treatments (B). EB, exploratory biomarker; PD, pharmacodynamic; PK, pharmacokinetic; 4F-PCC, four-factor prothrombin complex concentrate; TXA, tranexamic acid.
day 4 rivaroxaban dose. Both BD and BV were measured. Safety and tolerability were evaluated throughout the study. Safety assessments included adverse events (AEs), clinical laboratory tests, vital signs, 12-lead electrocardiograms, and physical examination findings.

Endpoints

For the randomized portion of the study (Part 2), the primary endpoints used to assess the effects of 4F-PCC and TXA on rivaroxaban at steady state included bleeding variables (BD and BV) and PD parameters (PT and thrombin generation assay [TGA]). The secondary endpoints were rivaroxaban pharmacokinetics (PK) at steady state and rivaroxaban safety and tolerability. Exploratory endpoints included levels of coagulation factors (FII, FVII, FIX, FX, protein C, and protein S) and biomarkers reflective of increased thrombin generation, including levels of F1+2, D-dimer, and thrombin–antithrombin complexes (TATs).

Blood samples for determination of either predose or trough rivaroxaban plasma levels were obtained via an indwelling catheter or direct venipuncture before each rivaroxaban administration on days 1–3 (Table S1). Additionally, serial blood samples for PK and PD assessments were collected after rivaroxaban administration on day 4 for up to 72 h (PK assessment) or 168 h (PD assessment). Blood samples for exploratory biomarkers were collected before and up to 168 h after rivaroxaban administration on day 4. For PK samples, blood was collected in EDTA-containing vacutainer tubes, and, after centrifugation (1300 g for 15 min or 1500–1600 g for 10 min) of the cellular elements, platelet-poor plasma was frozen in aliquots at −20 °C before shipment to the bioanalytic facility (PPD Laboratories, Middleton, WI, USA) for analysis with a validated, specific and sensitive tandem mass spectrometry method. The rivaroxaban maximum observed plasma concentration, minimum observed plasma concentration, trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose (C_{trough}), time to reach the maximum observed plasma concentration, and area under the plasma concentration–time curve during a dosing interval at steady state were computed from the individual plasma concentration versus time profiles with a non-compartmental approach. The primary PD variables assessed in this study were the PT and ETP from the TGA, and both were analyzed with validated methods at the respective laboratories. All PT measurements were performed with clot detection assays and the same PT reagent (freeze-dried thromboplastin from rabbit brain [Neoplastin Plus; Roche Diagnostics, Mannheim, Germany]) at LabCorp, Overland Park, KS, USA. Thrombin generation was measured with the Technochlor TGA assay (Technochlor, Vienna, Austria) at MedPace, Cincinnati, OH, USA. The data derived from the thrombograms were used to calculate the ETP (area under the thrombogram curve).

Punch biopsies were performed on day 1 (baseline) and day 4 (Fig. 1A), no earlier than 4 h (and no later than 4 h and 15 min) after the final rivaroxaban dose and according to the following protocol. After local administration of lidocaine without epinephrine, a disposable instrument was used to perform a standardized punch biopsy (5 mm in depth and diameter) on the back of the thigh. BV was assessed from blood absorbed onto preweighed filter papers every 30 s, without touching the edge of the wound. To limit evaporation during the collection procedure, filter papers were placed in sealed, humidified, preweighed containers. The blood-soaked filter papers used for each individual subject were weighed to determine BV. Bleeding from the wound was defined as having stopped when blood no longer stained the filter paper; BD was defined as the time elapsed from initial blood emergence at the wound to cessation of bleeding. On completion of the assessments, sutures were applied to close the wound at 25 min, even if bleeding had not stopped spontaneously.

Statistical analyses

All efficacy analyses were conducted in the per-protocol set. The safety analysis set included all subjects who received at least one rivaroxaban dose.

On the basis of the estimated intrasubject coefficient of variation (CV) for BD obtained from Part 1, and with the conservative assumption of a 30% intrasubject CV for BD for each treatment group in Part 2 of the study, a sample size of 48 subjects for each treatment group was considered to be sufficient for the 95% confidence interval (CI) for the BD mean ratio (post-treatment over baseline) to be within 80–125% with a power of 80%, on the assumption that the post-treatment/baseline ratio equals 95–105%.

The primary endpoints for the statistical analysis were the log-transformed BD and BV values for each treatment group. A mixed-effect model that includes time as a fixed effect and subjects as a random effect was used to estimate the least-squares means and intrasubject variance. From these estimated values, the point estimates and 95% CI for the difference in mean BD and BV values on a log scale between post-treatment and baseline were calculated for each treatment group. The means and limits of the CIs were retransformed by the use of antilogarithms to obtain geometric means and 95% CIs for the ratios of the geometric mean values for bleeding variables. Descriptive statistics of BD and BV values and change from baseline were summarized by treatment group.

Additionally, a mixed-effect model was fitted to the log-transformed change from baseline bleeding parameter data (BD and BV) as the dependent variable, and
treatment group as a fixed effect and subject as a random effect. By the use of these estimated least-squares means and estimated intersubject variance, the point estimate and 95% CIs for the difference in means on a log scale between test (4F-PCC and TXA) and reference (placebo) were constructed. The limits of the CIs were retransformed by the use of antilogarithms to obtain 95% CIs for the ratios of the mean values for bleeding parameters of the test to reference for each comparison of interest.

Descriptive statistics were used to summarize the rivaroxaban plasma concentration data and PK parameters for each treatment group separately. The rivaroxaban \( C_{\text{trough}} \) values were tabulated and visually inspected for the attainment of steady state. Individual, composite and mean concentration versus time profiles were plotted by treatment group by the use of both linear and semilogarithmic scales.

Descriptive statistics were used to summarize the PD parameters (PT and ETP) and exploratory biomarkers by treatment group at each measured time point. Mean values for each of the PD parameters and the biomarkers versus time were plotted for each treatment group.

**Results**

In all, 159 subjects were enrolled between September 2015 and June 2016; 12 in Part 1 and 147 in Part 2. All 12 subjects completed Part 1. Of the 147 subjects enrolled in Part 2 (49 in each of the three cohorts), 145 (98.6%) completed the study; one subject each in groups A and B withdrew (both for personal reasons) (Fig. 2). Most subjects enrolled were male (70.1%) and white (66.0%), with a median age of 28.0 years and a mean BMI of 25.0 kg m\(^{-2}\). Table S2 summarizes study participants’ baseline and demographic characteristics.

**Part 1**

**Effect on punch biopsy BD and BV of a single 20-mg dose of rivaroxaban**

At baseline (day \(-1\)), the mean BD was 9.4 min (range, 5.2–12.7 min). As compared with baseline values, there was an approximate doubling in BD (19.1 min; range, 10.8–25.0 min) with a geometric least-squares mean ratio of 201.4% (95% CI 161.9–250.5%) after a single 20-mg rivaroxaban dose. In comparison, the mean BV at baseline (day \(-1\) predose) was \(\approx\) 2.2 mL (range, 0.4–4.2 mL); this increased to \(\approx\) 4.4 mL (range, 1.5–9.0 mL), which was less than a doubling in volume, with a geometric least-squares mean ratio of 182.5% (95% CI 113.5–293.6%). Median BD and BV values were close to the geometric mean values. The intrasubject CVs for both BD and BV associated with the punch biopsy procedure was estimated to be 25% and 57%, respectively.

**Fig. 2.** Subject disposition. 4F-PCC, four-factor prothrombin complex concentrate; TXA, tranexamic acid.
Effect on PD parameters of a single 20-mg dose of rivaroxaban. The lag time and time to peak were prolonged at 3 h after rivaroxaban administration and gradually returned to pretreatment values at 24 h postdose. The mean ETP value decreased at 3 h postdose and began to return to baseline values within 10–12 h postdose.

PK parameters of a single 20-mg dose of rivaroxaban. The PK parameters derived after a single 20-mg rivaroxaban dose appear to be consistent with the results observed in earlier studies that assessed the same dosing regimen [8,12,13] in healthy volunteers. A summary of single 20-mg dose PK parameters of rivaroxaban is shown in Table S3.

Part 2

Bleeding variables (BD and BV) after administration of 20 mg of rivaroxaban twice daily to steady state and after infusion of 4F-PCC, TXA, or saline control. At prestudy baseline (day –1), before the administration of rivaroxaban, the mean BD values were 10.0 min (range, 3.8–15.0 min), 9.9 min (range, 3.7–15.0 min), and 9.3 min (range, 3.2–15.0 min) in subjects randomized into treatment groups A (4F-PCC), B (TXA), and C (saline control), respectively. The corresponding mean BV values were 2.7 mL (range, 0.7–13.4 mL), 2.5 mL (range, 0.4–11.3 mL), and 3.4 mL (range, 0.3–32.2 mL), respectively. On day 4, after administration of 20 mg of rivaroxaban twice daily to steady state and after administration of treatments in groups A, B, and C, the mean BD values were 17.7 min (range, 6.0–25.0 min), 17.8 min (range, 3.6–25.0 min), and 17.6 min (range, 6.4–25.0 min), respectively. The corresponding mean BV values were 4.1 mL (range, 0.1–14.3 mL), 4.5 mL (range, 0.2–14.0 mL), and 4.3 mL (range, 0.9–13.5 mL), respectively. Median BD and BV values were close to the geometric mean values. For each treatment group, these changes represented slightly less than a doubling of the mean BD, and BV changes were generally consistent with BD changes for all three groups (Fig. 3). No differences from saline control were observed in either baseline-adjusted BD or BV after administration of 4F-PCC or TXA (Fig. 4).

Effect of administration of 20 mg of rivaroxaban twice daily to steady state and infusion of 4F-PCC, TXA or saline control on PD parameters. After administration of 20 mg of rivaroxaban twice daily, the mean trough PT
values at steady state were approximately 18 s for sub-
jects in all three treatment groups – a 4.5-s increase from
the mean baseline value of 13.5 s. After the administra-
tion of the last rivaroxaban dose on the morning of
day 4, the maximum mean PT value increased to
≈ 25 s
in all three treatment groups. This value decreased by
≈ 4 s within 15 min of 4F-PCC administration, with mean
PT values remaining lower than those following sal-
ine control administration until ≈ 24 h postdose. In com-
parison, mean PT values did not change after TXA
administration (data not shown).

Effects of administration of 20 mg of rivaroxaban twice
daily to steady state and infusion of 4F-PCC, TXA, or sal-
ine control on exploratory biomarkers After administra-
tion of 4F-PCC, $F_1 + 2$ levels quickly increased, whereas
D-dimer levels did not. In contrast, the levels of $F_1 + 2$
and D-dimer were unchanged after administration of
TXA or saline control (Fig. 6A,B). There were small
increases in TAT levels after administration of 4F-PCC,
TXA, or saline control (Fig. 6C). There were marked
increases in the levels of FII, FX, protein C and protein S
after 4F-PCC administration, but no increase after TXA
or saline control administration (data not shown).

PK parameters of 20 mg of rivaroxaban administered
twice-daily to steady state Mean trough plasma concen-
tration values demonstrated that rivaroxaban reached
steady-state concentrations by day 3 of the study. Plasma
PK parameters for rivaroxaban at steady state on day 4
are shown in Table 1. In general, the mean steady-state
rivaroxaban plasma PK parameters were similar across
all three treatment groups, and were consistent with the
results observed in earlier studies that assessed the 20-mg
twice-daily dosing regimen in healthy volunteers [12].

Safety assessments There were no discontinuations because of AEs and no
deaths or treatment-emergent serious AEs (SAEs). Two
(1.4%) subjects in Part 2 withdrew early from the study
for personal reasons (Fig. 2).

The only treatment-emergent AEs (TEAEs) during
Part 1 were upper respiratory tract infection ($n = 2$) and
postprocedural hemorrhage ($n = 1$). The postprocedural
hemorrhage event reported in one subject resolved on the
next day when direct pressure was applied to the biopsy
site. The event was mild in severity and very likely related
to rivaroxaban. The most common TEAEs during Part 2
were nausea ($n = 19$), headache ($n = 16$), dizziness
($n = 10$), paresthesia ($n = 6$), contact dermatitis ($n = 5$),
gingival bleeding ($n = 4$), and epistaxis ($n = 4$). Most AEs
in Part 1 and Part 2 were mild in intensity, with the
exception of moderate-intensity menorrhagia ($n = 2$) and
nausea ($n = 1$) in Part 2. Both menorrhagia events
occurred on day 1 and were considered to be very likely
related to study drug administration. None of the changes
in hematology, serum chemistry or coagulation parameters (aPTT and PT) in Part 1 and Part 2 were considered to be clinically relevant; none of them was reported as a TEAE.

Discussion

This study used a punch biopsy bleeding model to assess the utility of 4F-PCC or TXA as potential reversal agents for rivaroxaban-induced bleeding. In volunteers pretreated with a supratherapeutic dose of rivaroxaban, neither 4F-PCC nor TXA attenuated bleeding from standardized punch biopsy sites. However, consistent with previous reports [7,8], 4F-PCC shortened the PT and increased the ETP, and was associated with an increase in the levels of $F_1 + 2$ and D-dimer – a finding that is consistent with a procoagulant state. Therefore, although 4F-PCC has the potential to reverse the PD effects of rivaroxaban, there is no guarantee that the effects observed on coagulation parameters will translate to effects on clinical bleeding and outcomes.

Unlike 4F-PCC, TXA had no effect on the PT or the ETP, nor did it induce a procoagulant state. Although TXA inhibits plasmin, thereby attenuating clot degradation, TXA had no effect on rivaroxaban-induced bleeding from punch biopsy sites. However, the skin is not rich in fibrinolytic activity, and our findings do not exclude the

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possibility that TXA could attenuate bleeding from other tissues, such as those that might be damaged after trauma or surgery. Therefore, TXA still might be of value to control bleeding related to increased fibrinolysis in rivaroxaban-treated patients presenting with major trauma or requiring surgical intervention.

Fig. 6. Changes in exploratory biomarkers by treatment group. Time course of (A) prothrombin fragment $1 + 2$ ($F_{1+2}$), (B) D-dimer and (C) thrombin–antithrombin complex (TAT) mean absolute value changes from baseline for treatment with four-factor prothrombin complex concentrate (4F-PCC), tranexamic acid (TXA), and saline control.

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The failure of 4F-PCC to reverse punch biopsy bleeding in volunteers given rivaroxaban is at odds with a recent report that the dose of 4F-PCC used in this study attenuated punch biopsy bleeding in volunteers given edoxaban, another oral FXa inhibitor [14]. However, it should be noted that, in previous studies with other anticoagulants and reversal agents, the punch biopsy model has yielded variable results [15,16]. Therefore, the punch biopsy data in this study should be interpreted with caution. Nevertheless, the PT and ETP changes in response to 4F-PCC observed in this study are consistent with those reported previously with both rivaroxaban and edoxaban [8,14,17]. Potential explanations for the difference in results from those of the edoxaban study include differences in the doses and drug regimens used in the two studies. Here, we gave supratherapeutic doses of rivaroxaban (20 mg twice daily) and dosed volunteers for several days to achieve high steady-state levels of rivaroxaban. In contrast, in the previous study, volunteers were given only a single 60-mg dose of edoxaban, which is the usual treatment dose. If 4F-PCC failed to reverse punch biopsy bleeding in volunteers given rivaroxaban because the regimen that we used resulted in higher rivaroxaban levels, bleeding should be attenuated by giving more 4F-PCC, or by using the current amount of 4F-PCC but reducing the dose of rivaroxaban. These possibilities need to be explored.

Finally, it is also possible that our findings reflect a type II error because of the large between-subject variability in BV (57%) and BD (25%) measurements after punch biopsy. A wide variability in bleeding profiles appears to be an inherent limitation of the punch biopsy model. A similar recent study with edoxaban, which employed the same punch biopsy model, also demonstrated considerable intrasubject variation (26–35% for BD and 36–38% for BV) [14]. Increasing the sample size would address this possibility. Additional studies are also needed to determine whether 4F-PCC attenuates punch biopsy bleeding when given in conjunction with TXA. In conclusion, this study demonstrates that neither 4F-PCC nor TXA reverses punch biopsy bleeding in volunteers given supratherapeutic doses of rivaroxaban. Nonetheless, 4F-PCC shortens the PT and increases the ETP and the levels of F1+2 and D-dimer. In contrast, TXA has no effect on these variables.

Finally, no deaths or treatment-emergent SAEs occurred during this study. None of the subjects withdrew from the study because of AEs. Overall, the AEs observed in this study were consistent with the known safety profile of rivaroxaban (Xarelto), and no new safety signals were identified. Although 4F-PCC reduced the PT and increased the ETP in volunteers given supratherapeutic doses of rivaroxaban, neither 4F-PCC nor TXA influenced punch biopsy bleeding.

**Addendum**

J. H. Levy, K. T. Moore, and J. I. Weitz designed the study, interpreted the results, wrote the manuscript, and critically reviewed the manuscript. M. D. Neal, D. Schneider, and V. S. Marcsisin interpreted the results, wrote the manuscript, and critically reviewed the manuscript. J. Ariyawansa designed the study, performed statistical analysis, interpreted the results, wrote the manuscript, and critically reviewed the manuscript.

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**Disclosure of Conflict of Interests**

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steering committees, data safety monitoring boards, and/or advisory boards for Boehringer-Ingelheim, CSL Behring, Grifols, Instrumentation Laboratories, Janssen, Leading Biosciences, Portola, and Pfizer. K. T. Moore, V. S. Marcisin and J. Ariyawansa are employed by Janssen. M. D. Neal has received research funding from Janssen and serves as an external scientific advisor, and has also served as a consultant to CSL Behring for unrelated studies. D. Schneider has received grants and honoraria from Bayer, Boehringer Ingelheim, Bristol-Myers-Squibb, Daiichi-Sankyo, Ionic Pharmaceuticals, Janssen, Merck, Portola, Novartis, and Pfizer.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Part 1 study design.
Table S1. Part 2 blood draw schedule.
Table S2. Demographic and baseline characteristics (safety analysis set).
Table S3. Summary of pharmacokinetic parameters of rivaroxaban in Part 1 (PK data analysis set).

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