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The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII in apixaban-treated patients in vitro

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Abstract

Background: The number of patients under treatment with FXa inhibitors is increasing, but there is no concensus on how to reverse their anticoagulant effect in case of a life-threatening bleeding. A specific antidote is not yet commercially available. Prothrombin complex concentrate (PCC), activated PCC (aPCC) and recombinant factor VIIa (rFVIIa) are suggested available reversal agents.

Objectives: To find the most effective reversal agent to apixaban and to determine the optimal dose.

Patients/Methods: PCC, aPCC, and rFVIIa at concentrations imitating 80%, 100%, and 125% of suggested therapeutic doses were added to blood drawn from apixaban-treated patients (n=30). aPCC was also tested in a 50% dose. Samples from healthy subjects (n=40) were used as controls. Thromboelastometry in whole blood (WB) and thrombin generation in platelet-poor plasma (PPP) were measured to assess the reversal effect.

Results: aPCC shortened clotting time (CT) in WB, and increased the peak thrombin concentration and velocity index in PPP to a greater extent than PCC and rFVIIa. No significant differences were seen between rFVIIa and aPCC on thrombin generation lag time, or between PCC and aPCC on endogenous thrombin potential (ETP). The 50% dose of aPCC had a slightly inferior effect, but was comparable to the other reversal agents.

Conclusions: In this in vitro study the 80% dose of aPCC (40 IU/kg) reversed the anticoagulant effect of apixaban more effectively than the corresponding dose of rFVIIa and PCC both in WB (CT) and PPP (peak, ETP).

KEYWORDS

activated prothrombin complex concentrate, apixaban, prothrombin complex concentrate, recombinant factor VIIa, reversal

Essentials

- An antidote for apixaban is not yet available.
- We tested the effect of different haemostatic agents to reverse the apixaban effect in vitro.
- Activated prothrombin complex concentrate (aPCC) was superior to prothrombin complex concentrate and recombinant activated factor VII.
- Even low doses of aPCC reversed the apixaban effect completely in vitro.

1 | INTRODUCTION

Direct-acting oral anticoagulants (DOACs), including the factor Xa (FXa) inhibitor apixaban, have been proven to be effective and safe alternatives to warfarin in treatment of thrombosis and prevention of stroke in patients with atrial fibrillation.[1,2] Although it is documented that the associated bleeding risk is lower for apixaban than for warfarin, spontaneous and trauma-induced bleeding episodes do occur.[3–5] As the prescription rate of DOACs is increasing, major bleeding episodes due to these drugs is not a negligible issue.

There is no concensus on how to reverse the anticoagulant effect of apixaban in a situation with a major bleed. Routines for supportive treatment are established, but the guidelines on how to reverse the anticoagulant effect of apixaban are inconsistent.[6–10]

A direct-acting reversal agent to apixaban is not yet available, but a specific antidote to FXa inhibitors, andexanet alpha, has been developed. A phase II clinical study recently demonstrated efficacy in reversing the anticoagulant effect, but also raised a concern regarding safety, especially the risk of thrombotic complications.[11] Until a specific antidote is commercially available, the toolbox in case of a major bleed comprises of prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (aPCC) and recombinant factor VIIa (rFVIIa). However, the efficacy of these reversal agents is not well documented and the optimal dosage is unknown. Four-factor PCC has most commonly been used to reverse the effect of vitamin K antagonists, replacing coagulation factors II, VII, IX, and X in their zymogen or inactive forms.[12] Activated PCC contains factor (F) VII, mainly in the activated form, and FII, FIX, and FX, mainly in non-activated forms. aPCC and rFVIIa are both primarily licensed for the treatment of haemophilia patients with inhibitors.[13–15] All three agents have been studied for their ability to reverse the anticoagulant effect of FXa inhibitors in vitro and in animal models.[16–22] Data from in vitro studies suggest that PCC has an inferior effect in reversing the anticoagulant effect of apixaban and rivaroxaban (thrombin generation assay) as compared with aPCC and rFVIIa.[16,19,21] Recently the current authors published an in vitro study where aPCC in a lower dose than recommended in guidelines had a superior effect reversing the rivaroxaban effect compared to PCC and rFVIIa.[22] In this study patients taking anticoagulation for therapeutic reasons were included. The amount of data about the ability of unspecific reversal agents to reverse the anticoagulant effect of apixaban in patients using apixaban for therapeutic reasons, however, is limited.

The aims of the present study were to compare PCC, aPCC, and rFVIIa as reversal agents ex vivo in blood drawn from patients treated with therapeutic doses of apixaban and to find the most effective dose of the reversing agents. We also wanted to investigate if an even lower dose of aPCC would be sufficient to reverse the apixaban effect.

2 | MATERIALS AND METHODS

2.1 | Study design

The design of a previous study performed by our group, was also used in the present study.[22] In the present study we used a different study population treated with a different anticoagulant. Base on the results for the previous study, a different dose of one of the haemostatic agents has also been evaluated.

2.2 | Participants

Thirty patients with a history of venous thromboembolic disease and treated with therapeutic doses of apixaban were recruited at the outpatient clinic for thrombosis at Akershus University Hospital. In addition, 40 healthy volunteers, mostly recruited from the staff at the hospital and research institute, served as controls. Inclusion criteria for patients were more than 4 weeks of treatment with apixaban 5 mg twice daily, the other inclusion- and exclusion criteria for study patients and controls were as described previously.[22] Written informed consent was given by all the participants, and the study was approved by the Norwegian regional committee for medical and health research ethics (approval no 2012/961).

2.3 | Haemostatic agents and doses

Four-factor PCC (Cofact, Sanquin, Amsterdam, the Netherlands), aPCC (FEIBA, Baxter AG, Vienna, Austria), and rFVIIa (Novoseven, NovoNordisk, Copenhagen, Denmark) were the reversal agents evaluated in this study in the same doses as described in previous work.[22] In addition to imitating 80%, 100%, and 125% of the doses suggested for clinical use in case of a major bleeding in a patient treated with a DOAC according to international guidelines[23] we also tested the 50% dose for aPCC in the current study. PCC was tested in doses equivalent to 32, 40, and 50 IU/kg, aPCC was tested in doses equivalent to 25, 40, 50 and 62.5 IU/kg and rFVIIa was tested in doses equivalent to 72, 90, and 112.5 μg/kg.

2.4 | Blood collection

Blood samples were collected using minimal stasis and a 21G × 19 mm butterfly needle (Vacuette Greiner Bio-One GmbH, Kremsmünster,

Austria) approximately 2 hours after drug intake, ie, at the time of the presumed peak concentration of apixaban in the patients. For measurements of thromboelastometry and thrombin generation, whole blood was collected in 10 mL tubes containing 1.0 mL with 0.109 M buffered citrate (Monovette, Sarstedt, Nümbrecht, Germany) that were manually prefilled with additional Corn Trypsin Inhibitor (CTI) (Haematologic Technologies, Incorporated, Essex Junction, VT, USA) at a final concentration of 20 μg/mL. Blood samples for anti-FXa measurements were collected in 4.5 mL Vacutainer tubes (Becton-Dickinson, Franklin Lakes, NJ, USA) containing 0.5 mL with 0.109 M buffered citrate without CTI.

2.5 | Preparations

The sampled whole blood from each patient was pooled and divided into 10 aliquots of 5 mL. PCC, aPCC, and rFVIIa were added to the different aliquots in the different doses, and to represent the baseline value, one aliquot was left untreated.

Aliquots of whole blood spiked with 3 different haemostatic agents at increasing concentrations and the untreated aliquot were incubated at 37°C for 30 minutes. Then the samples were further subdivided, and platelet-poor plasma (PPP) was prepared.

Platelet-poor plasma for thrombin generation assay was obtained by double centrifugation (10 min at 2000 *g* in room temperature [RT] and after careful removal of the supernatant another centrifugation for 10 minutes at 10 000 g in RT). PPP was immediately frozen and stored at −80°C for 1–3 months before measurements of thrombin generation.

The remaining whole blood was incubated at 37°C for another 30–90 min before performing measurements by thromboelastometry. For measurements of apixaban concentration, citrated plasma was prepared as described in previous work.[22]

2.6 | Thrombin generation assay (TGA) and thromboelastometry

Thrombin generation was measured in PPP using the same method as described earlier.[22,24,25] The method used for clotting in whole blood initiated with a low amount of TF was also described earlier.[22,26–28]

2.7 | Anti-FXa activity measurements

The apixaban concentration was measured in citrated plasma by an anti-FXa activity method. We used the anti-Xa assay Biophen Direct Xa Inhibitor DiXal (HYPHEN BioMed, Neiville-Sur-Oise, France) performed on the STA-R Evolution coagulometer (STAGO), according to the manufacturer's instructions.[29]

2.8 | Statistical analysis

To compare the effect of the haemostatic agents, analysis of variance (ANOVA-test) was used followed by the Tukey's test for multiple comparisons. Statistical calculations were performed by using SPSS version 21 (SPSS, Inc, Chicago, IL, USA), and statistical significance was set to $P<0.05$. Linear regression was used when assessing the relationship between the apixaban concentration and coagulation parameters. The data were expressed as mean value with a 95% confidence interval (CI) or one standard deviation (SD).

3 | RESULTS

From December 2015 to May 2016, 30 patients treated with apixaban were enrolled in the study. Forty healthy volunteers were recruited as controls.[22] All patients were using apixaban 5 mg twice daily for deep vein thrombosis and/or pulmonary embolism, and they were recruited at least 4 weeks after the acute thrombotic episode. The main characteristics of patients and controls are displayed in Table 1.

3.1 | Thrombin generation in platelet poor plasma

Apixaban affected all the thrombin generation parameters (Figure 1). Mean lag time was more than doubled compared to healthy controls, 6.5 minutes (95% CI 4.9-8.1) vs 2.9 minutes (95% CI 2.7-3.1). Peak height was reduced by 75%, 47 nM (95% CI 40-55) vs 194 (95% CI 171-217), velocity index by 80%, 11.8 nM/min (95% CI 9.3-14.4) versus 60.0 nM/min (95% CI 48.8-71.1), and ETP by approximately 30%, 886 nM*min (95% CI 779-993) versus 1269 nM*min (95% CI 1166-1373).

The prolonged lag time was not influenced by the addition of PCC (Figure 2A). aPCC, however, caused a shortening of the lag time by almost 39.4% (95% CI 33.8-45.2) in a 100% dose, and rFVIIa caused a shortening of the lag time by 48.9% (95% CI 43.6-54.3) in a 100% dose (Figure 2A). The difference in reversing effect between the two drugs (100% dose) was not statistically significant, and all doses of aPCC and rFVIIa had a similar reversing effect.

Peak thrombin concentration was increased by 111.6% (95% CI 98.7-124.5) by PCC (100% dose) compared to apixaban-treated patient samples with no haemostatic agent addded. The 100% dose of aPCC caused an increase of 353% (95% CI 295.1-410.1) which was significantly larger than the increase caused by the 100% dose of rFVIIa which was 145.3% (95% CI 115.6-175.0) (Figure 2B). For

TABLE 1 Characteristics of patients and controls

	Patients (n=30)	Controls (n=40)
Age, years	57.0 (17.6)	50.3 (12.8)
Weight, kg	84.3 (16.5)	–
Time after intake, mins	137 (7.1)	–
Apixaban dose (b.i.d)	5 mg	–
Gender (m/f), n/n	18/12	16/24
Deep vein thrombosis, n (%)	12 (40)	–
Pulmonary embolism, n (%)	18 (60)	–

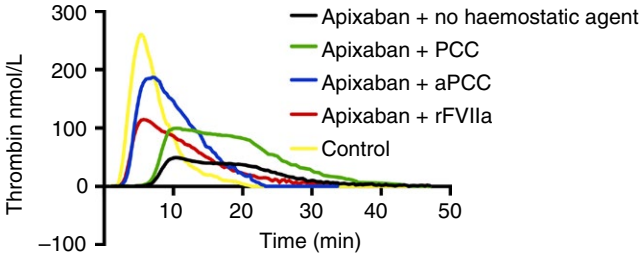

FIGURE 1 Reversal of the anticoagulant effect of apixaban by reversal agents shown in a representative thrombogram. A representative thrombogram of a control and an apixaban-treated patient with and without reversal agents is shown. The reversal agents in a 100% dose are shown: prothrombin complex concentrate (PCC) (40 IU/kg), activated PCC (aPCC) (50 IU/kg) and recombinant factor VIIa (rFVIIa) (90 μg/kg)

PCC and rFVIIa there was not a dose-response relationship between the different doses. The 100% dose of aPCC caused a significantly greater increase in peak concentration than the 50% dose (P<0.05), but there was not a statistical difference between the 125% dose and the 80% dose of aPCC (P=0.825). Only aPCC at the 125% concentration brought the mean peak concentration to above the level of normal controls.

The velocity index (VI) was increased by 25.4% (95% CI 2.1-48.6) by PCC (100% dose), 455.6% (95% CI 353.0-558.3) by aPCC (100% dose) and 332.0 (209.1-454.8) by rFVIIa (100% dose)(Figure 2C). aPCC and rFVIIa, in all doses, were more effective in increasing VI than PCC. aPCC and rFVIIa (100% dose) increased VI in a similar manner (P=0.71). All doses of aPCC, including the 50% dose, and rFVIIa had a similar reversing effect.

ETP was increased by 134% (95% CI 120-147) after addition of PCC (100% dose). Addition of aPCC (100% dose) caused an increase of 226% (95% CI 194-258) and rFVIIa (100% dose) caused an increase of 43% (95% CI 32-55) (Figure 2D). There was not a difference in the reversing effect between different doses of PCC (P=0.56 and P=0.25) or between different doses of rFVIIa (P=1.0 and P=1.0). aPCC in doses of 80%, 100% and 125% had a stronger reversing effect than PCC and rFVIIa (P<0.0001), and aPCC (80% dose) increased the ETP significantly

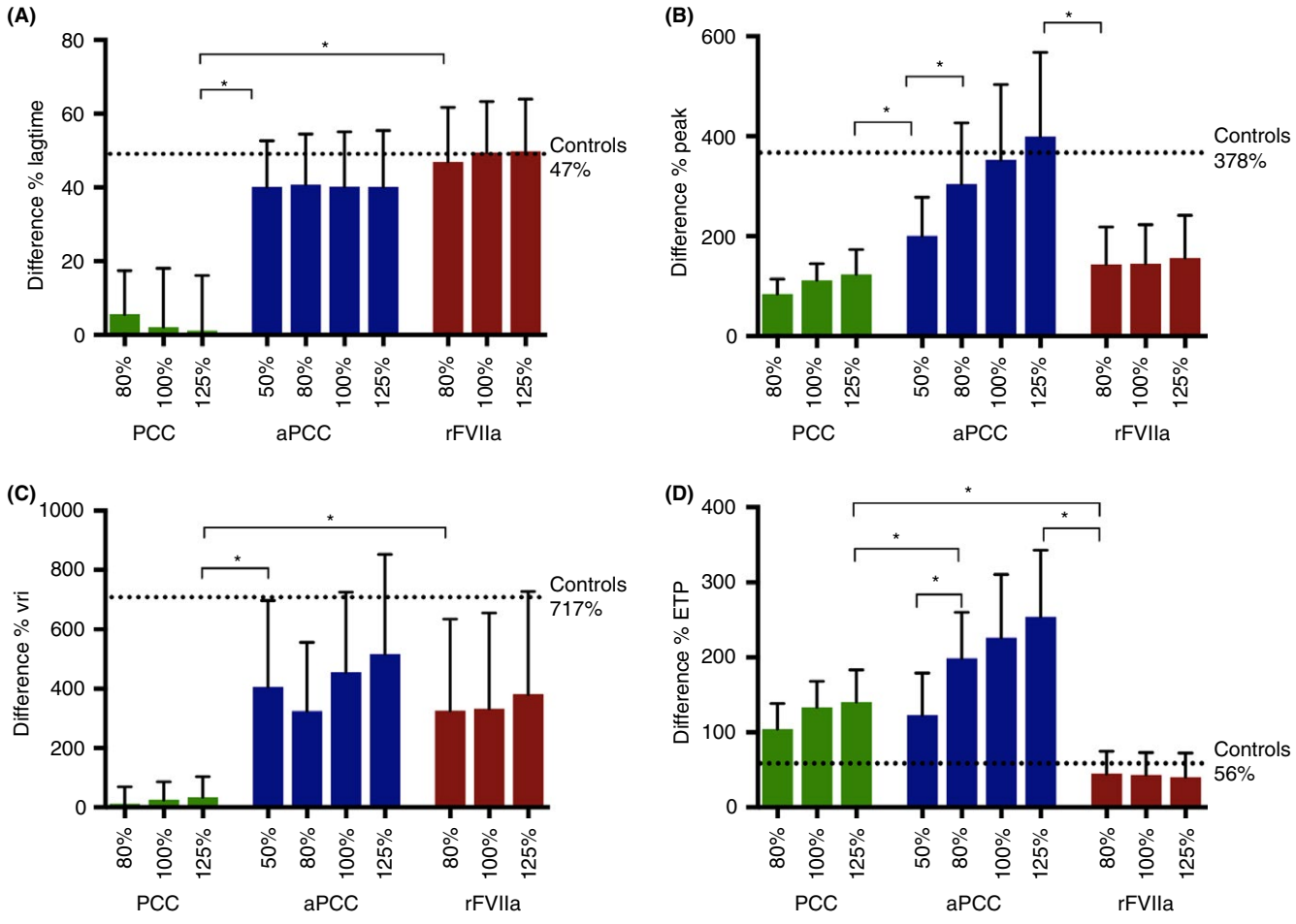

FIGURE 2 Difference in thrombin generation parameters after the addition of reversal agents in different doses to samples from apixaban-treated patients. Values are differences in percent between the baseline value (patient sample without the addition of a reversal agent) and the value obtained after the addition of a reversal agent in three different doses. (A) Lag time in platelet poor plasma (PPP) (minutes). (B) Peak height of thrombin in PPP (nM). (C) Velocity index in PPP (nM/min). (D) Endogenous Thrombin Potential (ETP) in PPP (nM*min). The control level is illustrated by the dotted line and represents the mean difference in percent between the patient baseline value and the mean value of the controls. *P<0.005. PCC, prothrombin complex concentrate; aPCC, activated PCC; rFVIIa, recombinant factor VIIa

TABLE 2 Thromboelastometry results in whole blood in apixaban-treated patients before the addition of haemostatic agents and in healthy controls

	Patients (SD)	Controls (SD)	*P*-value
Clotting time, seconds	1647 (790)	706 (198)	<0.001
Clot formation time, seconds	245 (130)	188 (40)	<0.001
Maximum clot firmness, mm	54.8 (11.5)	56.0 (5.2)	0.5

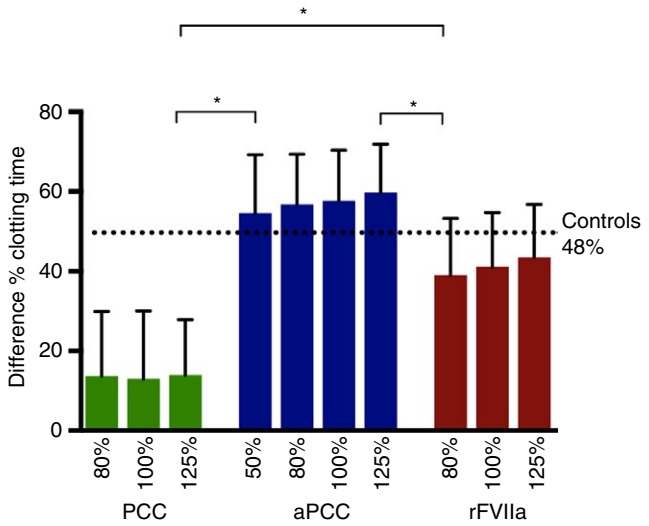

FIGURE 3 Differences in clotting time in whole blood (thromboelastometry) after the addition of reversal agents in different doses to samples from apixaban-treated patients. Values expressed as differences in percent between the baseline value (clotting time in the patient sample without the addition of a reversal agent) and the value obtained after the addition of a reversal agent in three different doses. The control level is illustrated by the dotted line and represents the mean difference in percent between the patient baseline clotting time and the mean clotting time of the controls (706 seconds). *P<0.005. PCC, prothrombin complex concentrate; aPCC, activated prothrombin complex concentrate; rFVIIa, recombinant Factor VIIa

more than a lower dose of aPCC (50% dose) (P<0.0001). There was not a significant difference between the reversing effect of aPCC (50% dose) and PCC (125% dose) (P=0.97). Both PCC and aPCC, in all doses, caused an increase of ETP that exceeded the mean control value.

3.2 | Thromboelastometry

Patients on apixaban had a significantly longer CT than the controls (Table 2). CT was more than doubled in apixaban-treated patients compared to the controls,1647 seconds (95% CI 1351-1942) vs 706 seconds (95% CI 643-769). Clot formation time was also prolonged in apixaban-treated patients, but maximum clot firmness was not affected.

Prothrombin complex concentrate (100% dose) caused a shortening of the CT by 14% (95% CI 8-20), aPCC (100% dose) caused a shortening of the CT by 58% (95% CI 53-63), and rFVIIa (100% dose) caused a shortening of the CT by 41% (95% CI 34-44). There was not a significant difference in the reversing effect between a dose of 80%, 100% and 125% for any of the haemostatic agents (P=1.00). aPCC in a dose of 80%, 100% and 125% was significantly more effective than the other drugs regardless of dose. The 50% dose of aPCC had a similar reversing effect as aPCC in higher doses (80%, 100%, and 125%) (P<0.0001). Furthermore, aPCC (50% dose) was more effective than PCC in all doses and also more effective than rFVIIa (80% and 100% dose) (P<0.05). The 50% dose of aPCC had similar reversing effect to the highest dose of rFVIIa (125% dose) (P=0.10) (Figure 3).

3.3 | Anti FXa-activity measurements

The mean apixaban concentration in the patient group was 174.5 ng/mL (95% CI 147.3-201.8). Apixaban concentrations were compared to CT in whole blood and to TG parameters in PPP. The correlation between the apixaban concentration and the CT in whole blood was moderate, but significant (ß=0.58, P=0.001) (Figure 4A). There was also a moderate negative correlation between the apixaban concentration and the peak thrombin concentration in PPP (ß=−0.58, P=0.001) (Figure 4B). The negative correlation between the apixaban concentration and the velocity index in PPP was weaker (ß=−0.43, P=0.02) (Figure 4C) as was the negative correlation between the apixaban levels and the ETP in PPP (ß=−0.47; P=0.01) (Figure 4D).

4 | DISCUSSION

In this in vitro study the ability of three different non-specific reversal agents to reverse the anticoagulant effect of apixaban in patients was evaluated. Different doses of PCC, aPCC, and rFVIIa were tested to imitate 80%, 100%, and 125% of the recommended doses in existing guidelines. For aPCC, we also included a dose of 50% (25 IU/kg) since previous work has shown a similar and strong reversing effect of aPCC for doses between 80% and 125% when the effect of another FXa inhibitor, i.e., rivaroxaban was reversed.[22] Not surprisingly, the results of the current study were similar to the study reversing rivaroxaban effect, as the 2 anticoagulants have the same mechanism of action. By using the recommended doses for aPCC, PCC, and rFVIIa, this study demonstrated that aPCC is a more effective reversal agent of apixaban than PCC and rFVIIa for many of the measured parameters. These results are consistent with previous studies.[16,19] Interestingly, in the present study we found that even the reduced dose of aPCC 50% (25 IU/kg) showed a greater efficacy than PCC both in reducing CT and lag time and in increasing the peak concentration and velocity index.

In this study we did not observe the same strong correlation between the FXa concentration and the tested thromboelastometry and thrombin generation parameters as in the previous rivaroxaban study.[22]

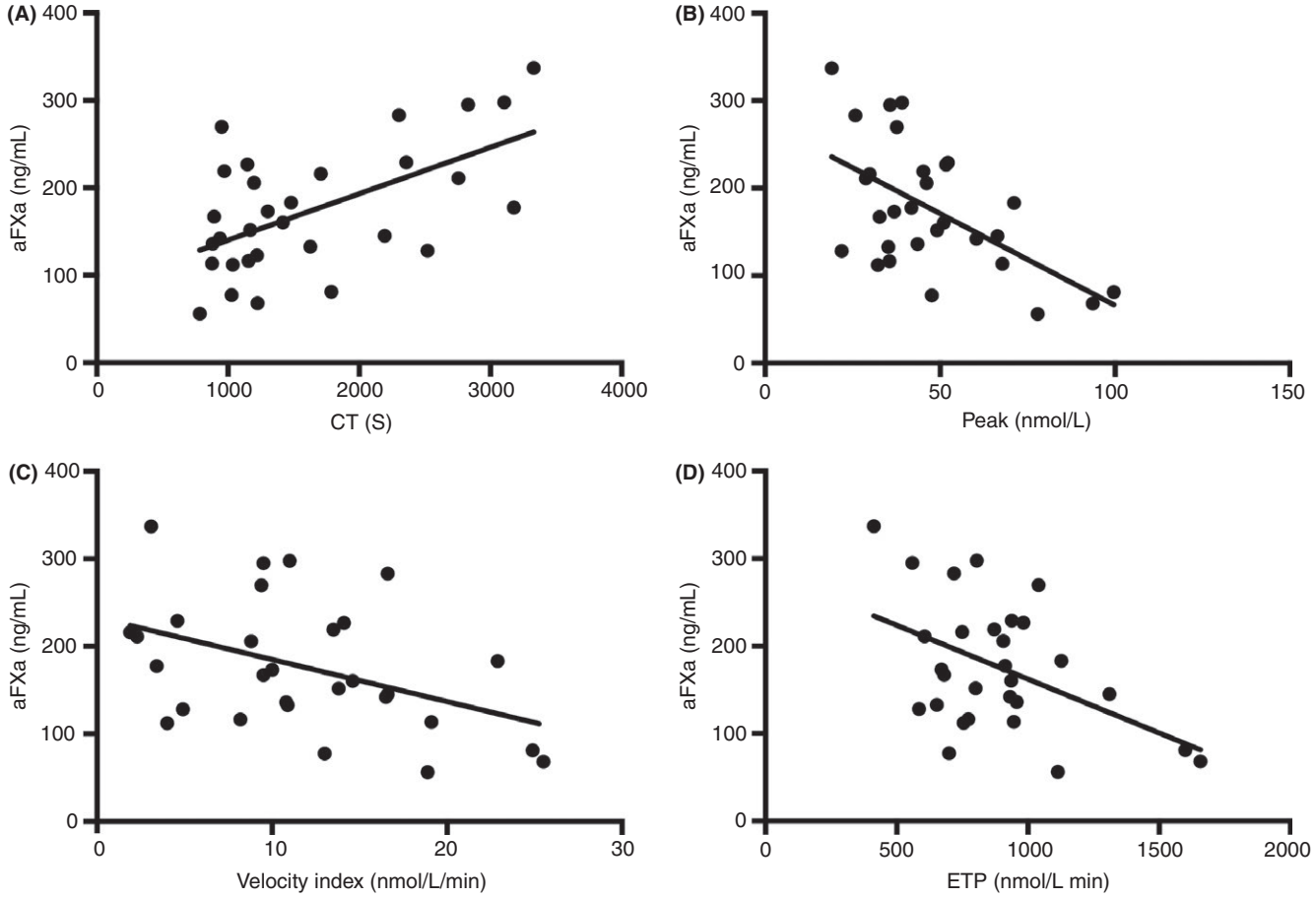

FIGURE 4 Correlation between apixaban concentration and coagulation parameters in apixaban- treated patients (n=30). (A) Correlation between the apixaban concentration and the clotting time (CT) in whole blood obtained by thromboelastometry. (ß=0.58, P=0.001). (B) Correlation between the apixaban concentration and the thrombin generation parameter peak height. (ß=−0.58, P=0.001). (C) Correlation between the apixaban concentration and the thrombin generation parameter velocity index. (ß=−0.43, P=0.02) (D) Correlation between the apixaban concentration and the endogenous thrombin potential (ETP). (ß=−0.47, P=0.01)

This is probaly related to the lower FXa concentrations in this study, as apixaban is administred twice instead of once daily.

The 4-factor PCC Cofact, which does not contain any heparin, was used in this study. However, protein C and protein S are present, which is not the case for the pure factor concentrates aPCC and rFVIIa. The content of protein C and protein S in PCC may be one possible reason for the reduced reversing effect of PCC, but it is not known whether this is the case in vivo.

PCC is often used as reversal agent in case of major bleeding due to DOACs, and this is partly due to findings in the study performed by Eerenberg et al. where the authors demonstrated that PCC was an effective reversal agent in vitro.[30] Another reason for why PCC is preferred might be the concerns for the thrombogenicity of factor concentrates containing activated coagulation factors[31–33], as apixaban-treated patients already have an increased risk of thromboembolic episodes. However, in the study by Eerenberg et al. aPCC was not tested and compared to PCC, and documentation on thromboembolic complications associated with reversal of the anticoagulant activity of DOACs is sparse. There are, however, several case reports where aPCC has been administrated to patients on DOACs, and in these cases an increased risk of thromboembolism was not observed. In the reported cases aPCC (FEIBA) in doses of 30-55 IU/kg was administrated to patients on DOACs with intracranial bleeding or abdominal aneurysm where immediate surgery was needed.[34–37]

Because of the thrombotic risk of administrating factor concentrates to patients with a history of thromboembolic disease, a lower dose of aPCC was tested (50% dose; 25 IU/kg) in this study. Compared to a dose of 80%, aPCC in a dose of 50% was not as efficient when comparing some of the thrombin generation parameters (peak value and ETP). However, compared to the other haemostatic reversing agents, aPCC in a dose of 50% was equal or more effective as a reversal agent when comparing thrombin generation parameters or CT.

Because conventional ROTEM tests are shown to be less sensitive to direct-acting FXa inhibitors, including apixaban, low-TF activated thromboelastometry method was used in this study.[26–28] In the study of Adelmann et al., this method was shown to be more sensitive than the conventional tests with a higher concentration of TF, but there was an overlap in CTs reported for patients and baseline values. This

was also the case in our study, but the results after addition of reversal agents seemed to be consistent. Furthermore, in the study of Adelmann et al. the baseline mean CT was shorter than the mean CT of the controls in our study. The reasons for the longer baseline CTs in our study may be due to the use of a different batch of Innovin TF, hence a lower final concentration, or the use of CTI in the samples in our study which inhibits coagulation activity initiated by contact activation.

There are limitations of this study. This is an in vitro study, and the measurements do not reflect the effect of apixaban nor the reversal agents in vivo completely. However, while previous studies are animal studies and studies performed on plasma from healthy volunteers, we included patients using apixaban for therapeutic reasons. All apixaban-treated patients had had a venous thrombotic episode, and the use of blood and plasma from these patients may reflect the in vivo situation more accurately than spiking blood and plasma from healthy subjects. In addition, in our study, several clinically relevant doses of the reversal agents were evaluated to find the optimal dosage. The findings of a moderately strong correlation between the measurements of the apixaban concentration (anti-FXa activity) and the parameters CT in whole blood (thromboelastometry), thrombin generation peak value and velocity index may indicate that the tests are relevant as markers of haemostasis in the patient.

aPCC, in a dose lower than suggested in the current guidelines, has in this in vitro study demonstrated to be a more effective reversal agent of apixaban than the recommended doses of PCC and rFVIIa. This might therefore be the preferred treatment in an emergency situation with a life-threatening bleeding in an apixaban-treated patient. However, because of the risk of thromboembolic complications administrating a factor concentrate to reverse the effect of anticoagulants should be limited to situations with a major or life-threatening bleeding episode where an effective reversal is crucial.

AUTHOR CONTRIBUTIONS

NH Schultz performed the experiments, interpreted the data and drafted the manuscript. HTT Tran planned the study and contributed to the manuscript. S Bjornsen performed the experiments, supervised in the laboratory work and contributed to the manuscript. PM Sandset and CE Henriksson contributed to the research process and revised the manuscript. PA Holme planned the study, analysed the data and revised the manuscript.

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RELATIONSHIP DISCLOSURES

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REFERENCES

1. Agnelli G, Buller HR, Cohen A, et al. AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799–808.
2. Yeh CH, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. Arterioscler Thromb Vasc Biol. 2015;35:1056–65.
3. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
4. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124:2450–8.
5. Touma L, Filion KB, Atallah R, Eberg M, Eisenberg MJ. A meta-analysis of randomized controlled trials of the risk of bleeding with apixaban versus vitamin K antagonists. Am J Cardiol. 2015;115:533–41.
6. Ageno W, Büller HR, Falanga A, et al. Managing reversal of direct oral anticoagulants in emergency situations. Anticoagulation Education Task Force White Paper. Thromb Haemost. 2016;116:1003–10.
7. Kaatz S, Kouides PA, Garcia DA, et al. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. Am J Hematol. 2012;87(Suppl 1):S141–5.
8. Levi M. Management of bleeding in patients treated with direct oral anticoagulants. Crit Care. 2016;20:249.
9. Pernod G, Albaladejo P, Godier A, et al. [Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors. Proposals of the Working Group on Perioperative Haemostasis (GIHP) - March 2013]. Ann Fr Anesth Reanim. 2013;32:691–700.
10. Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. J Thromb Thrombolysis. 2013;35:391–8.
11. Siegal DM, Curnutte JT, Connolly SJ, et al. Andexanet Alfa for the reversal of factor Xa inhibitor activity. N Engl J Med. 2015;373:2413–24.
12. Chai-Adisaksopha C, Hillis C, Siegal DM, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. Thromb Haemost. 2016;116:879–90.
13. Luu H, Ewenstein B. FEIBA safety profile in multiple modes of clinical and home-therapy application. Haemophilia. 2004;10(Suppl 2):10–6.
14. Zhou ZY, Hay JW. Efficacy of bypassing agents in patients with hemophilia and inhibitors: a systematic review and meta-analysis. Clin Ther. 2012;34:434–45.
15. Tiede A, Amano K, Ma A, et al. The use of recombinant activated factor VII in patients with aquired haemophilia. Blood Rev. 2015;29(Suppl 1):19–25.
16. Escolar G, Fernandez-Gallego V, Arellano-Rodrigo E, et al. Reversal of apixaban induced alterations in hemostasis by different coagulation factor concentrates: significance of studies in vitro with circulating human blood. PLoS ONE. 2013;8:e78696.
17. Escolar G, Arellano-Rodrigo E, Lopez-Vilchez I, et al. Reversal of rivaroxaban-induced alterations on hemostasis by different coagulation factor concentrates - in vitro studies with steady and circulating human blood. Circ J. 2015;79:331–8.
18. Korber MK, Langer E, Ziemer S, Perzborn E, Gericke C, Heymann Cv. Measurement and reversal of prophylactic and therapeutic peak levels of rivaroxaban: an in vitro study. Clin Appl Thromb Hemost. 2014;20:735–40.
19. Martin AC, Gouin-Thibault I, Siquret V, et al. Multimodal assessment of non-specific hemostatic agents for apixaban reversal. J Thromb Haemost. 2015;13:426–36.
20. Perzborn E, Gruber A, Tinel H, et al. Reversal of rivaroxaban anticoagulation by haemostatic agents in rats and primates. Thromb Haemost. 2013;110:162–72.

21. Perzborn E, Heitmeier S, Laux V, Buchmüller A. Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor VII in vitro. Thromb Res. 2014;133:671–81.
22. Schultz NH, Tran HT, Bjornsen S, Henriksson CE, Sandset PM, Holme PA. The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII against anticogulation effect of Xa inhibitor. Thrombosis J. 2017;15:6.
23. Weitz JI, Quinlan DJ, Eikelboom JW. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation. 2012;126:2428–32.
24. Hemker HC, Giesen P, Al Dieri R, et al. Calibrated automated thrombin generation measurement in clotting plasma. Pathophysiol Haemost Thromb. 2003;33:4–15.
25. Hemker HC, Al Dieri R, De Smedt E, Béguin S. Thrombin generation, a function test of the haemostatic-thrombotic system. Thromb Haemost. 2006;96:553–61.
26. Casutt M, Konrad C, Schuepfer G. Effect of rivaroxaban on blood coagulation using the viscoelastic coagulation test ROTEM. Anaesthesist. 2012;61:948–53.
27. Adelmann D, Wiegele M, Wohlgemuth RK, et al. Measuring the activity of apixaban and rivaroxaban with rotational thrombelastometry. Thromb Res. 2014;134:918–23.
28. Sørensen B, Johansen P, Christiansen K, Woelke M, Ingerslev J. Whole blood coagulation thrombelastographic profiles employing minimal tissue factor activation. J Thromb Haemost. 2003;1:551–8.
29. Becker RC, Yang H, Barrett Y, et al. Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban–an oral, direct and selective factor Xa inhibitor. J Thromb Thrombolysis. 2011;32:183–7.
30. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation. 2011;124:1573–9.
31. Köhler M, Hellstern P, Lechler E, Uberfuhr P, Müller-Berghaus G. Thromboembolic complications associated with the use of prothrombin complex and factor IX concentrates. Thromb Haemost. 1998;80:399–402.
32. Aledort LM. Factor VIII inhibitor bypassing activity (FEIBA) - addressing safety issues. Haemophilia. 2008;14:39–43.
33. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. JAMA. 2006;295:293–8.
34. Messana E, Wilson SS. Activated Pcc (Feiba) for reversal of rivaroxaban-induced life-threatening bleeding–a case series. Crit Care Med. 2015;43:303.
35. Maurice-Szamburski A, Graillon T, Bruder N. Favorable outcome after a subdural hematoma treated with feiba in a 77-year- old patient treated by rivaroxaban. J Neurosurg Anesthesiol. 2014;26:183–183.
36. Kiraly A, Lyden A, Periyanayagam U, Chan J, Pang PS. Management of hemorrhage complicated by novel oral anticoagulants in the emergency department: case report from the northwestern emergency medicine residency. Am J Ther. 2013;20:300–6.
37. Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA. The role of FEIBA in reversing novel oral anticoagulants in intracerebral hemorrhage. Neurocrit Care. 2016;24:413–9.

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