Prothrombin Complex Concentrate Is Effective in Treating the Anticoagulant Effects of Dabigatran in a Porcine Polytrauma Model

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ABSTRACT

Background: In the event of trauma, emergency reversal of anticoagulation therapy may be required. However, no specific reversal agents are routinely available for the direct oral anticoagulants such as dabigatran. The authors investigated four-factor prothrombin complex concentrate (PCC) for treating dabigatran-induced anticoagulation in a porcine polytrauma model.

Methods: Dabigatran etexilate was given orally for 3 days and intravenously on day 4 to 32 pigs. Animals were randomized 1:1:1:1 to PCC (25, 50, or 100 U/kg) or saline. Study medication was administered 12 min after bilateral femur fractures and blunt liver injury. The primary endpoint was blood loss at 300 min.

Results: The mean plasma concentration of dabigatran was 487 ± 161 ng/ml after intravenous administration. Blood loss was 3,855 ± 258 ml in controls and 3,588 ± 241 ml in the PCC25 group. In the PCC50 and PCC100 groups, blood loss was significantly lower: 1,749 ± 47 ml and 1,692 ± 97 ml, respectively. PCC50 and PCC100 effectively reduced dabigatran’s effects on coagulation parameters, whereas control and (to a lesser extent) PCC25 animals developed severe coagulopathy. Sustained increases in endogenous thrombin potential occurred with PCC50 and PCC100.

Conclusion: Four-factor PCC (50 or 100 U/kg) is effective in reducing blood loss in dabigatran-anticoagulated pigs, but higher doses may induce a procoagulant state. (Anesthesiology 2015; 123:1350–61)

Excessive bleeding is the main cause of death among patients with trauma. This is related to the fact that 25 to 35% of trauma patients present with trauma-induced coagulopathy,1,2 a key aspect of which is reduced levels of coagulation factors. Goal-directed coagulation management with administration of coagulation factor concentrates based on viscoelastic coagulation monitoring has been proposed as a means of reducing patients’ exposure to allogeneic blood products and improving patient outcomes.3 The primary coagulation factor concentrates used for managing bleeding in trauma patients are fibrinogen concentrate and prothrombin complex concentrate (PCC).

A proportion of trauma patients presenting with coagulopathy may also be receiving anticoagulant medication, which can exacerbate the coagulopathy, further increasing the patient’s risk of bleeding; for example, a large population of individuals receive long-term treatment with vitamin K antagonists such as warfarin. Established evidence-based guidelines for the management of trauma in these patients recommend PCCs for emergency reversal of vitamin K antagonists.4–6 More recently, the availability of direct oral anticoagulants has changed the paradigm of anticoagulation. The intention of these drugs is to reduce the risk of bleeding-related complications. The direct thrombin inhibitor dabigatran, which inhibits free and clot-bound thrombin, was the first direct oral anticoagulant licensed for prevention and treatment of stroke in patients with nonvalvular atrial fibrillation in 2010.7 Results from the Randomized Evaluation of Long-term Anticoagulant TherapY (RE-LY) trial suggest a low overall risk of bleeding complications with dabigatran.8 Compared with warfarin, dabigatran etexilate (DE) 110 mg two times per day was associated with decreased

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removing dabigatran from the circulation. This approach continuous venovenous hemofiltration may be considered for emergency surgery, among individuals under dabigatran treatment.

Given orally to 32 male German Landrace pigs (mean body sited supply of water. Animals were anesthetized, prepared, procedure, was followed by overnight fasting with an unlimited amount of water. Acclimatization took place for a minimum of 10 days. However, as yet there are few data to support the use of PCC for dabigatran reversal.

Using a lethal polytrauma model of coagulopathy, we investigated the safety and efficacy of three doses of a four-factor PCC administered in vivo to dabigatran-anticoagulated pigs. The primary study endpoint was total blood loss after trauma.

Materials and Methods

Ethics and Anesthesia

This study was performed at the RWTH Aachen University Hospital, Aachen, Germany. All experiments were designed in accordance with German legislation governing animal studies, which follows the Guide for the Care and Use of Laboratory Animals. Official permission was granted from the appropriate government office for animal care and use (Landesamt für Natur, Umwelt und Verbraucherschutz, Recklinghausen; No. 84, April 2, 2013, A083). Before surgery, pigs were housed in ventilated rooms and allowed to acclimatize to their surroundings for a minimum of 10 days. Examination by a veterinarian ensured good health of all animals.

Dabigatran etexilate (30 mg/kg two times per day) was given orally to 32 male German Landrace pigs (mean body weight: 42 ± 5 kg; range: 39 to 45 kg) for 3 days before surgery. The last dose, administered 12 h before the surgical procedure, was followed by overnight fasting with an unlimited amount of water. Animals were anesthetized, prepared, and monitored as described previously.

Surgical Preparation

After line placement, a midline laparotomy with cystoscopy was performed. Subsequently, a 90-min infusion of dabigatran (0.77 mg kg⁻¹ h⁻¹ for 30 min and then 0.2 mg kg⁻¹ h⁻¹ for 60 min) was started. By using sealed envelopes, animals were randomized 1:1:1:1 to receive normal saline solution (control) or 25, 50, or 100 U/kg PCC (BeriReplex P/N; CSL Behring, Germany; U.S. brand-name Kcentra; Lot 80970111A). Before the infliction of injury, the infusion of dabigatran was stopped.

Injury Phase and PCC Application

After localization of the femur with a needle, a captive bolt gun (Karl Schermer & Co., Germany) was used to fracture both femurs and create a soft-tissue injury at the midshaft. Next, a reproducible blunt liver injury was induced using a custom-made instrument described elsewhere. Five minutes after injury, all animals received a fluid bolus of 5 ml kg⁻¹ min⁻¹ for 5 min, followed by continuous infusion at 40 ml kg⁻¹ h⁻¹ until 120 min postinjury and then 20 ml kg⁻¹ h⁻¹ until the end of the experiment. Twelve minutes postinjury, administration of study medication was initiated (saline or PCC, according to randomization). PCC was prepared according to the manufacturer’s instructions and infused at a rate of 10 ml/min. Also, at 12 min postinjury, the abdomen was reopened for blood loss measurement and to perform standardized hepatic packing.

The observation period ended 300 min after injury. Animals surviving for 300 min were euthanized with pentobarbital. Immediately after death, the abdomen was reopened, the vena cava was clamped cranially to the liver, and the intraperitoneal blood was collected to determine the total blood loss postinjury. Internal organs (heart, lungs, liver, and kidneys) were removed, fixed in formalin, and examined in toto (macroscopically) and in subsections (histologically) for the occurrence of thromboembolic events.

Blood Sampling and Analytical Methods

Blood samples were obtained before oral DE, before infusion of dabigatran, after 90 min infusion of dabigatran, and 12, 30, 60, 120, 180, and 300 min after injury. For animals dying before 300 min postinjury, the last sample was obtained immediately after death.

Hemoglobin concentrations were measured with a blood gas analyzer (ABL720; Radiometer, Denmark). Prothrombin time (PT; Innovin), fibrinogen concentration (thrombin reagent), and D-dimers were determined by standard laboratory methods using the appropriate tests (all from Siemens, Germany) on a BCS XP coagulation analyzer (Siemens). Activated partial thromboplastin time (aPTT; C. K. Prest®; Diagnostica Stago, France) test was performed on a CL4 coagulation analyzer (Behnk Elektronik GmbH & Co. KG, Germany). Thrombin–antithrombin (TAT) complexes (Enzygnost; Siemens) and fibrinopeptide A (FPA; Zymutest FPA; HyphenBiomed, France) were quantified by enzyme-linked immunosorption assays. Plasma concentrations of dabigatran were determined using diluted thrombin.
time (Hemoclot; HyphenBiomed). Activated cloting time (ACT) was measured using an i-Stat point-of-care device (Abbott Point of Care, USA) with celite cartridges.

**Thromboelastometry and Thrombin Generation**

Coagulation was assessed in whole blood by performing extrinsic- and intrinsic-activated thromboelastometry (EXTEM and INTEM, respectively) on a ROTEM® device (Tem International GmbH, Germany). The following parameters were measured: clotting time (CT, in seconds), clot formation time (CFT, in seconds), and maximum clot firmness (MCF, in millimeters).

Thrombin generation in plasma was measured using the Calibrated Automated Thrombogram (Thrombinoscope BV, The Netherlands), using final concentrations of 20 pM tissue factor and 4 pM phospholipids as described previously. The following parameters were assessed: endogenous thrombin potential (ETP), maximum thrombin generation (peak height), and time before thrombin generation occurred (lag time).

**Pathologic Examination**

Immediately after death, internal organs (heart, lungs, liver, and kidneys) were removed and fixed in 10% buffered formalin. All fixed organs were cut into slices (5 mm thickness) and examined by a pathologist who was unaware of treatment assignment. Examinations were performed mainly to evaluate any thromboembolic changes and to assess the degree of liver injury, as described previously.

**Statistical Analysis**

Power analysis was carried out *a priori* for detection of a significant difference in blood loss (the primary endpoint) between the study groups. Considering data from previous animal experiments performed by our group, the inclusion of four groups in this study, an estimated medium effect size (δ = 0.5), and a significance level of 0.05, a sample size of eight animals per group was sufficient to achieve a power of 0.84. Statistical analysis was performed using SPSS 22 (SPSS, USA). Differences between groups in total blood loss were assessed using ANOVA, with *post hoc* Tukey adjustment. For comparison of coagulation parameters, blood cell count and hemodynamic variables, a repeated-measure ANOVA was used with intervention as group factor and time as repeated factor. For significant effects or interactions, Sidak testing was used *post hoc*. Pairwise log-rank tests were used for survival analysis. Statistical tests were performed two tailed, and *P* values less than 0.05 were considered as statistically significant.

**Results**

**Impact of Oral Administration of DE and Intravenous Infusion of Dabigatran**

After 3 days of oral DE, the overall mean plasma concentration of dabigatran was 194 ± 96 ng/ml (study group values shown in table 1). Laboratory coagulation parameters were prolonged compared with baseline: PT from 8.6 ± 0.7 to 10.6 ± 1.7 s, aPTT from 15.1 ± 2.3 to 25.7 ± 5.3 s, and ACT from 121 ± 20 to 185 ± 43 s (fig. 1). Accordingly, the EXTEM and INTEM variables CT and CFT were also substantially prolonged (fig. 2). However, oral DE had no significant effects on clot strength (maximum clot firmness) or concentrations of hemoglobin, platelets, or fibrinogen (fig. 2 and table 1). After 90 min infusion of dabigatran, the overall mean plasma concentration of dabigatran increased to the supratherapeutic level of 487 ± 161 ng/ml. This was associated with further prolongation of PT, aPTT, ACT, and the EXTEM and INTEM variables CT and CFT (figs. 1 and 2). Dabigatran infusion also decreased overall thrombin generation (ETP; 110 ± 49 vs. 267 ± 86 nM·min after oral DE; *P* < 0.0001), decreased maximum thrombin generation (peak height; 13 ± 14 vs. 90 ± 42 nM; *P* < 0.0001), and prolonged the lag time (4.6 ± 1.1 vs. 3.1 ± 1.2 min; *P* < 0.0001) (study group data shown in fig. 3). However, dabigatran had no effects on D-dimers or TAT levels (fig. 4).

**Measurements after Induction of Standardized Injuries**

**Blood Loss and Survival.** Twelve minutes after injury, blood loss was similar in all four groups (overall mean: 783 ± 47 ml) (fig. 5). The primary endpoint of total blood loss was highest among control (3,855 ± 258 ml) and PCC25 (3,588 ± 241 ml) animals. Total blood loss was significantly lower among animals receiving the two higher doses of PCC (PCC50: 1,749 ± 47 ml and PCC100: 1,692 ± 97 ml; *P* < 0.0001 for both groups vs. either control or PCC25). Mortality rate was 100% in the control group, with a mean duration of survival of 100 min (range: 62 to 148 min) compared with 174 min (range: 65 to 275 min) in the PCC25 group. All animals in both PCC100 and PCC50 groups survived until the end of the observation period.

**Control Group Findings.** The control animals developed severe coagulopathy with prolongation of PT, aPTT, and the thromboelastometry parameters CT and CFT (figs. 1 and 2). These parameters deteriorated over time, resulting in significant prolongation compared with animals receiving PCC. There was no significant between-group difference in fibrinogen concentration. However, platelet count, clot strength (EXTEM and INTEM), and hemoglobin concentration were significantly lower in control animals than in the PCC50 and PCC100 groups (table 1 and fig. 2). Unlike animals in the PCC50 and PCC100 groups, control animals developed severe hemorrhagic shock with increasing levels of lactate (table 2). Accordingly, animals in the control group had significantly lower mean arterial pressure, lower cardiac output, and higher heart rate than animals in the PCC50 and PCC100 groups (table 2).

**Effects of 25 U/kg PCC.** Several coagulation parameters improved immediately after administration of 25 U/kg PCC. Significant decreases in INTEM CT, EXTEM CT, and INTEM CFT (fig. 2) were observed at 30 min postinjury...
in PCC25 group when compared with control animals, and ETP showed a significant increase at the same timepoint (fig. 3). With ongoing blood loss, thromboelastometry parameters and PT were slightly prolonged as compared to higher doses of PCC at 60 min after trauma, and the magnitude of these differences subsequently increased over time. There were no significant differences in platelet count or hemoglobin concentration between control and PCC25 animals (table 1).

Hemorrhagic shock was evident in the PCC25 group due to hemodynamic variables (e.g., low cardiac output and pulmonary arterial pressure) and increasing lactate levels (table 2). However, lactate concentration was significantly lower in the PCC25 group than in the control animals at 120 min posttrauma, suggesting that shock may have been less severe with PCC25 than control. The administration of 25 U/kg PCC had no significant impact on ACT or aPTT when compared with control (fig. 1).

Effects of 50 U/kg PCC or 100 U/kg PCC. Coagulation parameters (e.g., PT, aPTT, and INTEM/EXTEM CT and CFT) showed that PCC50 and PCC100 rapidly reduced the effects of dabigatran, with a similar degree of improvement in the two groups (figs. 1 and 2). Significant improvements were observed with PCC50 and PCC100 groups as compared to PCC25 and control animals. Corresponding with

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Data are mean ± SD; n = 8 for each data point except control group (120 min posttrauma), n = 3; PCC25 group (120 min posttrauma), n = 5; and PCC25 group (180 min posttrauma), n = 4.

* P < 0.05 vs. PCC50 and PCC100; † P < 0.05 vs. PCC100.

Hb = hemoglobin; PCC = prothrombin complex concentrate; Plt = platelet count.
significant reductions in blood loss, hemodynamic parameters remained stable in the PCC50 and PCC100 groups after fluid resuscitation and trauma. Shock-related parameters such as lactate concentration were also comparable among PCC50 and PCC100 animals (table 2). However, after PCC infusion, levels of TAT complex, D-dimers, and FPA increased dose-dependently, and levels remained highest in the PCC100 group until 300 min postinjury (fig. 4). The substantial increase in D-dimers in PCC100 animals up to 150,279 ng/ml (at 180 min) was associated with a trend toward lower plasma fibrinogen levels from 120 min postinjury, relative to the lower PCC doses, despite termination of bleeding. In addition, aPTT (fig. 1) and INTEM CFT (fig. 2) showed signs of prolongation in the PCC100 group after 120 min postinjury, suggesting consumption of coagulation factors as occurs in disseminated intravascular coagulation (DIC).18 Levels of platelets, hemoglobin, and antithrombin decreased initially after trauma and then remained constant in the PCC50 and PCC100 groups. Thrombin generation increased dose-dependently immediately after PCC administration. At 30 min after trauma, ETP was 870 ± 331 nM*min in the PCC50 group and 2,099 ± 587 nM*min in the PCC100 group, whereas peak height was 178 ± 69 nM and 386 ± 39 nM in the two groups, respectively (fig. 3). ETP remained above baseline throughout the remainder of the observation period in both PCC50 and PCC100 animals. Peak height remained similar to the baseline value in the PCC50 group. In the PCC100 group, peak height initially increased to a level approximately 2.5-fold above baseline and subsequently decreased over time while maintaining levels almost double the baseline value.

**Histopathologic Analysis**

The histopathologic examination of injured liver sections revealed homogeneous tissue damage and comparable lacerations of venous vessels up to 4 mm in diameter in all animals. Examination of kidneys, lungs, heart, and nontraumatized liver tissue showed no evidence of thromboemboli or DIC: there were no remarkable histopathologic changes in either controls or PCC-treated animals.

**Discussion**

This preclinical trial is the first to show that a four-factor PCC is effective in reducing the blood loss in dabigatran- and trauma-induced coagulopathy in a large animal model. At doses of 50 and 100 U/kg, PCC produced a significant reduction in blood loss and improved hemostasis. At the lower dose of 25 U/kg, PCC was not effective in reducing total blood loss postinjury under dabigatran anticoagulation. These results imply that a threshold level of prothrombin is needed to overcome dabigatran-induced thrombin inhibition and that this level is dependent on the concentration of dabigatran. However, high-dose PCC (100 U/kg) led to overcorrection of thrombin generation and

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**Fig. 1.** Standard laboratory coagulation tests. (A) Prothrombin time, (B) activated partial thromboplastin time (aPTT), and (C) activated clotting time (ACT). Data shown as mean ± SD; n = 8 for each data point except “all animals,” n = 32; control group (120 min posttrauma), n = 3; PCC25 group (120 min posttrauma), n = 5; and PCC25 group (180 min posttrauma), n = 4. BL = baseline; HD = high dabigatran (after oral administration); LD = low dabigatran (after oral administration); PCC = prothrombin complex concentrate. *P < 0.05 versus PCC50 and PCC100; †P < 0.05 versus PCC100; ‡P < 0.05 versus all PCC doses; §P < 0.05 versus PCC50.
Fig. 2. Thromboelastometry parameters. Extrinsically activated thromboelastometric test (activator: tissue factor) (EXTEM) and intrinsically activated thromboelastometric test (activator: ellagic acid) (INTEM) were performed according to the manufacturer’s instructions. Clotting time (CT; A and B) represents the initiation of clot formation. Clot formation time (CFT; C and D) represents the time between clot initiation and attainment of an amplitude of 20 mm; EXTEM CFT was not measurable in controls at 120 min posttrauma. Maximum clot firmness (MCF; E and F) reflects the strength of the clot that is formed. Data are shown as mean ± SD; n = 8 for each data point except “all animals,” n = 32; control group (120 min posttrauma), n = 3; PCC25 group (120 min posttrauma), n = 5; and PCC25 group (180 min posttrauma), n = 4. BL = baseline; HD = high dabigatran (after infusion); LD = low dabigatran (after oral administration); PCC = prothrombin complex concentrate. *P < 0.05 versus PCC50 and PCC100; †P < 0.05 versus PCC100; ‡P < 0.05 versus all PCC doses.
correspondingly increased TAT levels with increased fibrin formation. The increase in D-dimers also suggested secondary hyperfibrinolysis.

Our finding that PCC can, at an appropriate dose (50 U/kg with the level of anticoagulation in this model), be effective in treating coagulopathy without excessive activation of coagulation is in agreement with several previous animal studies, as well as limited experience in humans. In trauma-associated bleeding with dabigatran anticoagulation, increasing thrombin levels to the point that thrombin molecules outnumber dabigatran molecules should, theoretically, overcome the inhibitory effect of dabigatran. Because prothrombin in PCC is converted to thrombin, this would seem to be a plausible mechanism by which PCC may overcome dabigatran anticoagulation. PCC would only be effective when the dose is high enough to increase the plasma thrombin concentration above that of dabigatran. The observation that low-dose PCC (25 U/kg) is insufficient to overcome the dabigatran-induced coagulopathy in our porcine model is therefore consistent with the proposed mechanism of action. A similar degree of dose-dependency was previously observed with PCC treatment of dabigatran-induced anticoagulation in a rat tail bleeding model. Additional preclinical ex vivo studies, including both three- and four-factor PCCs, have provided further evidence of the need for a threshold thrombin concentration to be achieved. These previous studies included investigation of six different PCCs, and the degree of dose-dependency concerning reduction of the effects of dabigatran was similar with all of them. However, the impact of PCC on a relevant clinical endpoint such as blood loss was not evaluated in these studies.

In the current study, despite an initial increase in thrombin generation after administration of 25 U/kg PCC, subsequent loss of blood and reduction in thrombin generation were observed. Furthermore, plasma concentrations of fibrinogen decreased as a result of blood loss, fibrinolysis, consumption, and dilution. Fibrinogen is the first coagulation factor to reach critically low concentrations when bleeding occurs, and the results of several studies imply that the early application of fibrinogen may reduce blood loss. Previous studies have shown that fibrinogen and thrombin are key regulators in maintaining sufficient hemostasis in the absence of anticoagulation reversal. In addition, early administration of antifibrinolytic medication (e.g., tranexamic acid) is recognized as beneficial for trauma patients. Thus, when treating trauma patients who are receiving dabigatran therapy, it is possible that early administration of fibrinogen and antifibrinolytic medication could reduce the dose of PCC that is required.

The propensity of PCCs to increase thrombin generation is the key to their efficacy, but it may also be the key to the risk of thromboembolic events. Excessive concentrations of prothrombin (factor II) in relation to antithrombin have been suggested as the cause of thromboembolic complications.
Fig. 4. Markers of coagulation activation and inhibition. Levels of (A) thrombin–antithrombin complex (TAT) and (B) fibrinopeptide A reflect the activation of coagulation, whereas levels of (C) antithrombin and (D) D-dimers reflect inhibition of coagulation. Data are shown as mean ± SD; n = 8 for each data point except “all animals,” n = 32; control group (120 min posttrauma), n = 3; PCC25 group (120 min posttrauma), n = 5; and PCC25 group (180 min posttrauma), n = 4. BL = baseline; HD = high dabigatran (after infusion); LD = low dabigatran (after oral administration); PCC = prothrombin complex concentrate. *P < 0.05 versus PCC50 and PCC100; †P < 0.05 versus PCC100.

Fig. 5. Blood loss and survival. (A) Blood loss measured at 12 min (before intervention) and 300 min after injury. Data are shown as scatter plots (n = 8 for each study group), with horizontal lines representing mean and vertical lines representing interquartile range. (B) Survival data are presented as a Kaplan–Meier curve. PCC = prothrombin complex concentrate. *P < 0.05 versus PCC50 and PCC100.
This hypothesis corresponds with in vitro and in vivo data identifying prothrombin overload (and insufficient inhibition of newly generated thrombin by antithrombin) as the most likely cause of thrombosis.33,34 We have shown in an experimental animal model of liver injury without anticoagulation that 50 U/kg PCC may increase the risk of DIC, attributable to an imbalance of procoagulant and anticoagulant proteins.35 These data are in line with those from an observational, clinical study of four-factor PCC in severely injured patients.36 Although no thromboembolic complications were observed, the ETP was increased for several days, and this is expected to increase patients’ prothrombotic risk. The duration for which ETP was increased was observed by the authors to be consistent with the approximately 60-h half-life of prothrombin.36 In our study, despite high plasma concentrations of dabigatran and subsequent inhibition of thrombin generation, animals receiving 100 U/kg PCC exhibited generalized activation of coagulation and secondary hyperfibrinolysis.

Trauma is associated with increased fibrinolytic activity, with increased D-dimer levels after injury identified in many studies.37,38 Local activation of fibrinolysis occurs as tissue...
plasminogen activator is released from the endothelium after injury and ischemia.39-41 In addition, activation of the protein C pathway by thrombin bound to thrombomodulin leads to consumption of plasminogen activator inhibitor-1.42 Studies in severely traumatized patients with shock have shown that hypoperfusion is associated with increased levels of soluble thrombomodulin and decreased protein C.33-34 In the current study, increased levels of D-dimers and thrombin generation in PCC50 and PCC100 animals were dose-dependent, indicating that the excess thrombin may cause further activation of protein C and consumption of plasminogen activator inhibitor-1, resulting in systemic hyperfibrinolysis. Previous thrombin generation studies indicated that patients with acute trauma-induced coagulopathy have dysregulated hemostasis with site-of-injury–independent thrombin generation mediated by microparticles.43 Against this background, treatment with potent thrombin generators such as PCCs in traumatized patients with massive bleeding (with or without anticoagulation) should be titrated after an initial low dose (e.g., 20 to 30 U/kg), as opposed to administering a high dose initially.

A study in healthy volunteers reported a lack of reversal of dabigatran anticoagulation after administration of 50 U/kg PCC, with measurement of four different coagulation parameters.46 This result initially appears to contradict the current study, but the results may be explained by the study methods. The volunteers recruited by Eerenberg et al. were young and healthy with no coagulopathy, and blood loss was not included as an outcome measure. In contrast, the pigs in our study had undergone trauma and were bleeding heavily when they were treated with PCC, reflecting conditions under which emergency reversal of dabigatran may be required. As shown previously,13 two of the four parameters assessed by Eerenberg et al.46 (aPTT and thrombin generation lag time) were found in the current study to have low sensitivity to the effects of PCC in reducing dabigatran anticoagulation. The remaining two parameters assessed by Eerenberg et al., thrombin time and ecarin CT, are insensitive to the effects of PCC because of the activation of thrombin or prothrombin by the assay reagents.21

There is currently no widely available, validated measurement of dabigatran anticoagulation that also measures reversal. This complicates the treatment of bleeding patients requiring urgent intervention. Although the aPTT can provide an approximate indication of dabigatran anticoagulation and is extensively available, it appears to have limited sensitivity to the addition of PCCs. Certain laboratory-based coagulation tests such as diluted thrombin time and ecarin CT may have the potential to guide treatment of dabigatran-induced anticoagulation. Notably, in the current study, the thrombin generation assay showed a clear, dose-dependent increase in thrombin generation after PCC administration. The activation of coagulation was also evident after PCC administration from significant increases in TAT levels and FPA concentrations. However, some of these tests are not available in all hospitals, and they usually have slow turnaround times. In emergency surgery and/or trauma-related coagulopathy, delays in the detection of coagulopathy may impair treatment outcomes. In contrast to laboratory-based tests, thromboelastometry (ROTEM) and thrombelastography allow rapid assessment of coagulation status at the point of care. The EXTEM assay is similar to PT in that it assesses tissue factor–initiated extrinsic coagulation, theoretically making it the most suitable ROTEM assay for guiding PCC treatment of dabigatran anticoagulation. However, these tests are also not available in all hospitals, and none of the ROTEM parameters included in this study indicated a hypercoagulable state after PCC infusion. Also, ROTEM assays are not calibrated to measure the anticoagulant effects of dabigatran or their reversal. Thus, there is an urgent need for the development of new point-of-care devices to guide PCC therapy for dabigatran-induced anticoagulation.

Several limitations of our study need to be acknowledged. Trauma was induced in healthy, anesthetized pigs. Physiologic responses to factors such as pain and inflammation, and the presence of any comorbidities, may have additional effects on hemostasis; such factors are not reflected in our model. Perhaps most importantly, species differences mean that clinical trials are needed to confirm applicability of our study findings to human patients. The doses of dabigatran administered in this study were considerably higher than those typically administered to humans; further studies will be needed to determine the most appropriate doses of PCC for reversing therapeutic levels of dabigatran in humans.

In conclusion, coagulopathy associated with dabigatran anticoagulation and trauma was reduced in this study by early administration of PCC at doses of 50 and 100 U/kg. Blood loss was reduced and the survival rate was increased among animals receiving this treatment. However, the results also show that high-dose PCC (100 U/kg) can induce a prothrombotic state with substantial activation of coagulation and hyperfibrinolysis. Given the lack of clinical safety data for PCCs in this setting, the present data provide the best available insight. Appropriately titrated doses of PCC could potentially be considered as a therapeutic option to control life-threatening bleeding among dabigatran-treated patients. Studies in human patients are needed to evaluate the clinical safety and efficacy of PCC in this setting.

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Competing Interests
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