**Supplemental information: Methods**

Blood gases were measured on a blood gas analyzer (ABL700, Radiometer, Copenhagen, Denmark) using heparinized blood samples. Hemoglobin and platelets were measured in samples collected in potassium-EDTA-anticoagulant tubes (1.9 mg/mL final concentration, Sarstedt, Nuembrecht, Germany) using a standard hematology analyzer (MEK-6108, Nihon Kohden, Rosbach, Germany). For coagulation assays and measurement of plasma drug concentrations, blood was collected in 3.2% sodium citrate (Sarstedt) and potassium-EDTA-anticoagulant (1.9 mg/mL final concentration, Sarstedt), respectively, centrifuged to obtain platelet poor plasma and stored at ‑80°C until assayed. Prothrombin time (PT, Innovin® reagent), diluted thrombin time (dTT, Hyphen BioMed, Neuville sur-Oise, France) and D-dimer levels (Innovance® D-dimer assay) were determined by standard laboratory methods using a BCS XP analyzer (Siemens, Erlangen, Germany). Activated partial thromboplastin time (aPTT, CK Prest®, Diagnostica Stago, Asnieres sur Seine, France) and fibrinogen levels (Dade®, Siemens Healthcare, Marburg, Germany) were measured using standard methods with a CL4 coagulation analyzer (Behnk Elektronik GmbH &Co. KG, Norderstedt, Germany). Before determining fibrinogen, all plasma samples were incubated with 3 mg/mL idarucizumab to neutralize dabigatran concentrations in the sample. Thrombin–antithrombin (TAT) complexes and FPA were quantified by ELISAs (Enzygnost TAT, Dade Behring, Marburg, Germany; Zymutest FPA, Hyphen BioMed, Neuville-sur-Oise,France).

**Plasma concentrations of dabigatran**

Plasma concentrations of active dabigatran were determined by the calibrated diluted thrombin time (Hemoclot, HyphenBiomed, Neuville sur-Oise, France). The calibration curve was generated by spiking pooled porcine plasma with known amounts of dabigatran and then performing the assay according to the manufacturer’s instructions.

**Whole-blood assays: thromboelastometry and activated clotting time**

Whole-blood thromboelastometry was performed on a ROTEM analyzer (TEM International GmbH, Munich, Germany) according to the manufacturer’s instructions using blood samples collected in 3.2% sodium citrate. An extrinsically activated assay using recombinant tissue factor (EXTEM) and an intrinsically activated test using ellagic acid and phospholipids   
(INTEM) were used. The parameters assessed were clotting time (CT, sec), clot formation   
time (CFT, sec), and maximum clot firmness (MCF, mm).

Non-anticoagulated whole-blood samples were collected for measurement of activated   
clotting time (ACT) using an i-STAT point-of-care device (Abbott, Princeton, NJ) with celite cartridges.

**Thrombin generation**

Thrombin generation was determined in plasma using calibrated automated thrombinography (Thrombinoscope BV, Maastricht, The Netherlands) using 5 pM tissue factor (1, 2). Thrombin generation curves were generated using Thrombinoscope software (version 4, Thrombinoscope BV) to determine endogenous thrombin potential (ETP), lag time and peak thrombin formation. Prolonged lag time values that could not be detected by the software were defined as not detectable.

**Histopathologic analysis**

After death, internal organs (heart, lungs, liver, and kidneys) were removed immediately and fixed in 10% buffered formalin. Injured parts of the liver were cut into 3-mm-thick slices and examined macroscopically and microscopically by a pathologist blinded to therapy to assess the degree of injury. In addition, representative tissue sections of all 4 organs were   
processed to determine the occurrence of thromboembolic events. All samples were embedded in paraffin and stained, both by H&E and by a standard elastica van Gieson protocol, for histologic examination under light microscopy (Microscope: Nikon, Eclipse 50i; Lenses: Nikon, Plan Achromat, 2, NA0.06 [used for images with 20x magnification]; Nikon, Plan Achromat 4, NA 0.1 [used for images with 40x magnification]; and Nikon, Plan Fluor 40, NA0.75 [used for images with 400x magnification]). Both staining methods were applied to sections from all of the tissues. Sections of lung and liver tissue from regions with a high likelihood of thrombus formation were immunostained to test for fibrinogen (antibody and detection kit from Dako) as described elsewhere (3).

**Statistical analysis**

Statistical analysis was performed using SPSS 22 (SPSS, Chicago, IL) and GraphPad Prism 6.0h (GraphPad Software, La Jolla, USA) was used for graphing purposes. Differences in   
total blood loss between groups were assessed using analysis of variance, with post-hoc Tukey adjustment. For comparison of coagulation variables, blood cell count and hemodynamic variables, a repeated measure analysis of variance was used with intervention as group-factor and time as repeated-factor. The group by time interaction was also included to allow the group differences to vary over time. For significant effects, the Sidak method was used post-hoc. Pairwise log-rank tests were used for survival analysis. Statistical tests were performed two-tailed and P-values <0.05 were considered as statistically significant. Data are shown as mean ± standard deviation (SD).

**References**

1. Hemker HC, Giesen P, Al Dieri R, Regnault V, de Smedt E, Wagenvoord R, Lecompte T, Beguin S. Calibrated automated thrombin generation measurement in clotting plasma. Pathophysiol Haemost Thromb. 2003;33:4-15.
2. Spronk HM, Dielis AW, De Smedt E, van Oerle R, Fens D, Prins MH, Hamulyak K, ten Cate H. Assessment of thrombin generation II: Validation of the Calibrated Automated Thrombogram in platelet-poor plasma in a clinical laboratory. Thromb Haemost. 2008;100:362-364.
3. Grottke O, Braunschweig T, Spronk HM, Esch S, Rieg AD, van Oerle R, ten Cate H,   
   Fitzner C, Tolba R, Rossaint R. Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of   
   coagulopathy with blunt liver injury. Blood. 2011;118:1943-51.

**Supplemental table 1:** **Hemodynamic variables and** **lactate levels.** Data are shown as mean ± standard deviation (SD). In each group, n=9 animals initially. \*P<0.05 vs. control group; †P<0.05 vs. TXA–FCH group; ‡P<0.05 vs. PCC25 group. Between-group differences are presented hierarchically as follows: IDA and PCC50 (‡,†,\*)🡪 PCC25 (†,\*) 🡪 TXA–FCH (\*) 🡪 control.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | | Mean arterial pressure [mmHg] | Cardiac output [l/min] | Lactate  [mmol/L] |
| Baseline | | Control  TXA–FCH  PCC25  PCC50  IDA | —  —  —  —  — | —  —  —  —  — | 1.8 ± 0.7  1.7 ± 0.9  1.7 ± 0.5  1.2 ± 0.3  1.8 ± 1.3 |
| After dabigatran | | Control  TXA–FCH  PCC25  PCC50  IDA | 62 ± 2  61 ± 5  62 ± 4  62 ± 3  61 ± 3 | 3.7 ± 0.3  3.9 ± 0.5  4.0 ± 0.4  4.0 ± 0.3  3.9 ± 0.3 | 2.3 ± 0.2  1.8 ± 0.5  2.1 ± 0.7  1.9 ± 0.6  2.5 ± 0.3 |
| 12 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | 41 ± 7  46 ± 8  42 ± 4  43 ± 8  42 ± 5 | 3.0 ± 0.5  3.3 ± 0.5  3.5 ± 0.6  3.0 ± 1.0  3.5 ± 0.7 | 2.4 ± 0.3  2.1 ± 0.4  2.2 ± 0.5  2.1 ± 0.5  2.7 ± 0.2 |
| 30 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | 31 ± 7  35 ± 4  35 ± 8  46 ± 9\*†‡  54 ± 5\*†‡ | 2.3 ± 0.5  3.0 ± 0.3\*  3.1 ± 0.9\*  3.5 ± 0.5\*  4.1 ± 0.5\*†‡ | 3.1 ± 0.5  2.4 ± 0.3  3.4 ± 0.9  2.5 ± 0.7  3.0 ± 0.3 |
| 60 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | 28 ± 5  27 ± 4  36 ± 14  51 ± 9\*†‡  52 ± 4\*†‡ | 2.1 ± 0.5  2.6 ± 0.5  2.9 ± 0.9  3.7 ± 0.5\*†‡  4.0 ± 0.4\*†‡ | 5.5 ± 1.9  3.8 ± 1.3  3.8 ± 1.0  2.8 ± 0.8\*‡  2.9 ± 0.3\*‡ |
| 120 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | 17 ± 5  23 ± 7  43 ± 9\*†  51 ± 7\*†‡  50 ± 4\*†‡ | 1.0 ± 0.3  2.0 ± 0.9  3.4 ± 0.4  3.8 ± 0.5\*†‡  4.0 ± 0.5\*†‡ | 9.3 ± 2.0  7.9 ± 1.5  5.8 ± 3.2\*†  2.3 ± 0.5\*†‡  2.4 ± 0.4\*†‡ |
| 180 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | —  —  44 ± 9  51 ± 7‡  50 ± 4‡ | —  —  3.3 ± 0.4  3.7 ± 0.5  4.0 ± 0.5‡ | —  —  3.7 ± 1.3  1.9 ± 0.5‡  1.8 ± 0.5‡ |
| 240 min post-trauma | | Control  TXA–FCH  PCC25  PCC50  IDA | —  —  43 ± 7  53 ± 8‡  51 ± 5‡ | —  —  3.4 ± 0.4  3.8 ± 0.4  3.9 ± 0.5 | —  —  3.5 ± 2.1  1.5 ± 0.4‡  1.3 ± 0.3‡ |

Treatment groups: placebo [Control]; tranexamic acid (20 mg/kg) plus fibrinogen concentrate (80 mg/kg) [TXA–FCH]; prothrombin complex concentrate (25 IU/kg or 50 IU/kg) plus tranexamic acid plus fibrinogen concentrate [PCC25 and PCC50]; or 60 mg/kg idarucizumab plus tranexamic acid plus fibrinogen concentrate [IDA]

**Supplemental figure 1: Sub-analysis of animals in the PCC25 group, based on plasma dabigatran concentrations immediately after trauma (high concentrations, PCC25high; low concentrations, PCC25low).** Blood loss 12 minutes after liver injury but before intervention, and at the end of the experiment (240 minutes after liver injury) (**A**); survival data presented as a Kaplan-Meier curve (**B**); dabigatran levels **(C)**;endogenous thrombin potential (ETP) (**D**); prothrombin time (PT) (**E**); activated partial thromboplastin time (aPTT) (**F**). Data in plots C–F are shown as mean ± standard deviation. PCC25high, n=6; PCC25low, n=3.

