Supplemental Digital Content 1. Supplemental Methods

For measurement of whole blood thrombin time (1.5 and 3 U/mL), a 0.05 mL aliquot of each blood sample (37°C), was pipetted into the coagulometer. Thereafter, 0.1 mL of reagent (Bovine thrombin, OWHM 13, Siemens Healthcare, Marburg, Germany) was added (37°C) in order to initiate coagulation and the time (in seconds) was determined that elapsed from the addition of the reagent to the onset of blood clotting.

For whole blood activated partial thromboplastin time (aPTT), 0.05 mL of each native blood sample was pipetted into a test tube prewarmed to 37°C. To this, 0.05 mL of PTT reagent (Roche Diagnostics, Mannheim, Germany) was added, mixed and incubated for 3 min. Thereafter, 0.05 mL calcium chloride solution (37°C), was then added to initiate coagulation, and the aPTT was determined as the time elapsed (in seconds) between the addition of calcium chloride and the onset of clotting.

For whole blood prothrombin time, 0.05 mL of each native blood sample was pipetted into a test tube prewarmed to 37°C for 1 min. 0.1 mL of reagent (Thromborel S recombinant thromboplastin, Siemens Healthcare) was added (37°C) in order to initiate coagulation and the time (in seconds) that elapsed from the addition of reagent to the onset of blood clotting was determined.

For ecarin clotting time measurement, remaining rat whole blood was centrifuged to platelet poor plasma. Ecarin lyophilisate from echis carinatus snake venom was diluted in DBA-Buffer (Diethylbarbiturate-Acetate buffer solution, Dade Behring, Marburg, Germany) to a concentration of 15 U/mL and stored at room temperature (up to 8 h) until use. 0.05 mL of each plasma sample was pipetted into a test tube (37°C) for 1 min. 0.05 mL of DBA-buffer was added and incubated for 1 min. 0.05 mL of ecarin (5 U/mL final concentration, Sigma Aldrich Chemie,

Taufkirchen, Germany) was added in order to initiate coagulation and the time (in seconds) that elapsed from the addition of ecarin to the onset of plasma clotting was determined.

For the Hemoclot assay, plasma was diluted 1:8 in 0.15 M physiological solution (20 µl plasma + 140 µl physiological normal saline). 0.05 mL of the diluted plasma sample was pipetted into a test tube (37°C). 0.1 mL of normal pooled citrated plasma (Hyphen Biomed, Andresy, France) was added and incubated for exactly 1 min. 0.1 mL of human calcium thrombin, prewarmed to 37°C, was added in order to initiate coagulation and the time (in seconds) that elapsed from the addition of human calcium thrombin to the onset of plasma clotting was determined. A calibration curve was used to determine dabigatran plasma levels.