# Effective elimination of dabigatran by haemodialysis

## A phase I single-centre study in patients with end-stage renal disease

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**Summary**

Dabigatran, a specific, reversible direct thrombin inhibitor, is used to prevent ischaemic and haemorrhagic strokes in patients with atrial fibrillation. As with every anticoagulant, there is a need to rapidly reverse its effects in emergency situations. In an open-label, single-centre phase I study with two fixed multiple dosing periods, we investigated the pharmacokinetics, pharmacodynamics and safety of dabigatran before, during and after 4 hour haemodialysis sessions with either 200 or 400 ml/min targeted blood flow in seven end-stage renal disease patients without atrial fibrillation. Dabigatran was administered over three days in a regimen designed to achieve peak plasma concentrations comparable to those observed in atrial fibrillation patients receiving 150 mg b.i.d. and to attain adequate distribution of dabigatran in the central and peripheral compartments. Plasma concentration-time profiles were similar in both periods on Day 3 (Cmax: 176 and 159 ng/ml). Four hours of haemodialysis removed 48.8% and 59.3% of total dabigatran from the central compartment with 200 and 400 ml/minute targeted blood flow, respectively. The anticoagulant activity of dabigatran was linearly related to its plasma levels. There was a minor redistribution of dabigatran (<16%) after the end of the haemodialysis session. In conclusion, a 4 hour haemodialysis session can rapidly eliminate a substantial amount of dabigatran from the central compartment with a concomitant marked reduction in its anticoagulant activity. There was a clinically negligible redistribution of dabigatran after haemodialysis. These results demonstrate that haemodialysis can be a suitable approach to eliminate dabigatran in emergency situations.

**Keywords**

Dabigatran etexilate, direct thrombin inhibitor (DTI), pharmacokinetics, elimination, haemodialysis

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Clinical Trial Registration: EudraCT-Nr: 2010–021819–16 / NCT01241539.

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Received: August 21, 2012
Accepted after major revision: November 29, 2012
Prepublished online: February 7, 2013

**doi:10.1160/TH12-08-0573**
**Thromb Haemost 2013; 109: ■■■**

## Introduction

Vitamin K antagonists, i.e. inhibitors of vitamin K epoxide recycling into its active reduced form, have been widely and successfully employed for the prophylaxis and treatment of venous and arterial thromboembolic diseases for many decades. However, vitamin K antagonists have a number of clinically important drawbacks: 1) high intra-individual pharmacodynamic variability due in part to drug-drug and drug-food interactions; 2) high inter-individual variability in dose response; 3) slow on- and offset of action; 4) narrow therapeutic window; and 5) need for continual and frequent monitoring of the international normalised ratio (INR) and consequent dose adjustments (1, 2).

Dabigatran is a novel anticoagulant, acting via potent direct, reversible thrombin inhibition and it is the active moiety of the orally available prodrug dabigatran etexilate (DE) (3). Dabigatran does not require routine anticoagulation monitoring like vitamin K antagonists (4). DE has been approved for prophylaxis of venous thromboembolism (VTE) following surgical total knee or hip replacement in more than 70 countries as well as for the prevention of stroke in patients with non-valvular atrial fibrillation (AF) in Europe, North America and the Asia Pacific region (5-10). Dabigatran is characterised by no dietary interactions and few drug-drug interactions compared to warfarin (11). The drug has a half-life of 12–17 hours (h) in subjects with creatinine clearances above 60 ml/minute (min). It is predominantly eliminated via renal excretion (up to 80% of circulating dabigatran) without any active secretion or reabsorption by the renal tubules (12-16). For patients with a $Cl_{cr}$ < 30 ml/min (patients with severe renal insufficiency), its half life is roughly doubled (17).

The absence of a clinically available fast acting antidote or rapid elimination procedure is a major drawback for all anticoagulants

(3, 18). Clinical settings requiring a rapid reversal of any anticoagulant's activity may include major bleeding, the need for emergency surgery, acute kidney injury and overdosing (iatrogenic, accidental or in a suicidal attempt). Standard resuscitation approaches are currently used in these clinical settings for all anticoagulants (i.e. oral vitamin k antagonists, low-molecular-heparins and the novel oral anticoagulants; these include volume repletion, red cell, whole blood, and platelet (if thrombocytopenia is present) transfusions, repletion of coagulation factors and in more extreme cases use of activated factor VIIa). This is also described for patients who are treated with dabigatran (19).

Dabigatran has low plasma protein binding (approx. 30%), is highly water soluble and has an apparent volume of distribution of approx. 60-70 litres (11) and can, thus, be removed by haemodialysis (HD).

The present study was designed to determine the efficiency of a single optimised HD session in removing dabigatran from the circulation a) after $C_{max}$ levels had been achieved similar to those observed in patients with AF with normal renal function or mild renal impairment receiving 150 mg of DE twice daily (20) and b) adequate distribution of dabigatran between the central and peripheral compartment has been reached after multiple dosing. Due to the obligatory HD requirements in end-stage renal disease (ESRD) patients (here: HD 3 x weekly) definite steady state concentrations could not be reached. The primary objectives of this study were to determine the dialysis clearance from blood ($CL_{D,b}$) and from plasma ($CL_D$) and the rate of dabigatran removal from blood during standardised 4 h HD sessions with targeted blood flows of both 200 or 400 ml/min. Secondary objectives were the assessment of pharmacokinetic and pharmacodynamic parameters as well as subjects' safety and tolerability of the product in ESRD patients without AF and no or negligible renal dabigatran elimination (20).

## Methods

In an open-label, single-centre, multiple dose phase I study, we investigated the elimination, pharmacokinetics, pharmacodynamics, safety and tolerability of DE (Pradaxa®, Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim, Germany) after multiple dosing in a cohort of seven clinically stable ESRD patients. Ethical reasons restrict a much higher number of patients, as they were not eligible for kidney transplantation during the course of the study. More over minimum number of six patients was considered as sufficient to obtain precise estimates for the parameters of the primary objectives. This was because of the very low variability expected in the extraction ratio at the membrane. The extraction ratio, in its turn, is only dependent on flow rates and physicochemical properties of the membrane.

Primary objectives were blood and plasma dialysis clearance and the proportion of dabigatran removed from the central compartment during a standardised 4 h HD session. Secondary objectives were to evaluate pharmacokinetic measures (total [sum of free and dabigatran-glucuronide] and free dabigatran plasma concentrations post-dialysis and pre-dialysis; pre-dialysis pharmacokinetic parameters in the ESRD patient population with the defined dosing schedule); pharmacodynamics (activated partial thromboblastin time (aPTT) and the diluted thrombine time (dTT) and safety parameters. The study protocol (Eudract-Nr: 2010-021819-16) was reviewed and approved by an independent local ethical review board (Ethikkomission der Landesärztekammer, Berlin, Germany) and performed in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice and adhered to the ethical principles of the Declaration of Helsinki of the World Medical Association. All participants provided written informed consent.

### Study population

ESRD patients without atrial fibrillation aged between 21 to 60 years with a body mass index (BMI) between 18 to 30 kg/m$^2$ were eligible for study entry. ESRD patients had to be on HD three times a week (three sessions per week with one three-day interval) for at least three months with a residual urine volume of less than 500 ml/day. All study subjects had to be in clinically stable medical conditions for at least four weeks prior to trial entry as determined by past medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory assessments.

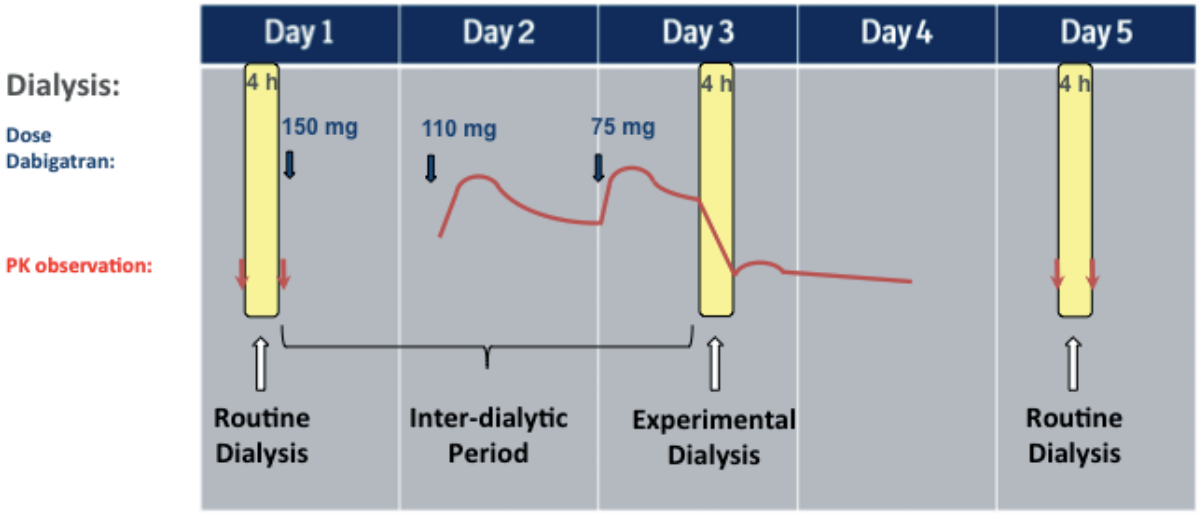
### Study protocol

ESRD study subjects enrolled went sequentially through a screening period and two dosing and elimination periods (Period 1 and 2). Those periods consisted of dosing and three HD elimination sessions, performed on Day 1, Day 3 and Day 5 of each period. Treatment periods were separated by a washout period of at least six weeks and followed by a study completion visit (►Figure 1). Pharmacokinetic simulation was used to define a dosing regimen in subjects with ESRD with minimal residual urinary output that would result in dabigatran plasma concentrations similar to those in patients with atrial fibrillation with mild on no renal impairment, receiving 150 mg of DE twice daily. Accordingly DE capsules were given to ESRD patients in the following regimen: 150 mg immediately after a regular HD on day 1 (0 h, start), 110 mg on Day 2 (21 h) and 75 mg (42 h) on Day 3. HD was performed on Day 1, before the first dose DE (-4 to 0 h), Day 3 (50-54 h, 8 h after last study drug dose) and Day 5 (91-95 h).

### Haemodialysis modalities

Standardised HD sessions were carried out using each patient's arteriovenous shunt. An overview of the HD modalities is given in ►Figure 1. All HD treatments were 4 h in duration, were performed with an AK 200 dialysis device (Gambro Hospal GmbH, Gröbenzell, Germany) and a bicarbonate-based dialysate. Prior to DE dosing on Day 1 of each dosing and elimination period, a standard HD treatment was carried out (blood flow 300 ml/min, dialysate flow 500 ml/min, Polyflux PF-140H dialyser, surface 1.4 m$^2$, Gambro Dialysatoren GmbH, Hechingen, Germany and heparin-




| Hemodialysis modalities | DAY 1 | DAY 3 | DAY 5 |
|---|---|---|---|
| Dialysate Flow Rate, [ml/min] | | | |
| Period 1 | 500 | 700 | 700 |
| Period 2 | 500 | 700 | 700 |
| Blood Flow Rate, [ml/min], targeted | | | |
| Period 1 | 300 | 200 | 300 |
| Period 2 | 300 | 400 | 300 |
| HD membrane used | Polyflux PF-140H dialyser | Polyflux PF-210H dialyser | Polyflux PF-210H dialyser |
| HD heparin anticoagulation | 2000 IU bolus + 1000 IU per h | 1000 IU bolus + 500 IU per h | 2000 IU bolus + 1000 IU per h |

**Figure 1: Overview of study flow and summary of haemodialysis modalities.**

based anticoagulation with 2,000 IU as bolus followed by 1,000 IU per h; ▶Figure 1).

On Day 3, after the third DE was administered, a HD setting was employed that maximised elimination by selecting the largest and most adequate membrane available (based on dabigatran's physic-chemical properties) and choosing the largest dialysate flow rate possible. This included a maximal dialysate flow rate of 700 ml/min and high flux filters with an extra-large surface of 2.1 $m^2$ (PF-210H, Gambro). In the first dabigatran dosing and elimination period, a blood flow rate of 200 ml/min was targeted. This flow rate reflects the clinical situation when a central venous catheter would be in place for potential use as an access port for HD and when blood flow rates up to 200 ml/min could reasonably be expected ("catheter setting"). During the second dosing and elimination period period, blood flow rates of 400 ml/min were targeted. This setting resembles the clinical situation in an ESRD patient with an available dialysis shunt ("shunt setting"). If a blood flow of 400 ml/min could not be achieved, the maximal tolerable blood flow was attained. In both catheter and shunt dialysis settings, a low-dose heparin anticoagulation scheme was used to ensure effective HD while keeping the patients bleeding risk low (1,000 IU heparin bolus followed by 500 IU per hour; ▶Figure 1).

On Day 5 of each dosing and elimination period, an "adapted" regular HD was performed. The adaptations compared to the regular HD on Day 1 comprised a dialysate flow of 700 ml/min, PF-210H dialyser and standard anticoagulation with heparin (2,000 IU bolus followed by 1,000 IU per h). Only the blood flow of 300 ml/min remained unchanged (▶Figure 1).

## Sample collection and analytical method

Twenty-six venous blood samples for PK and/or PD evaluations were taken through an indwelling catheter at baseline [pre-dose (0 h) on Day 1] through 95 h post-dosing on Day 5. During the HD session on Day 3, blood samples were collected at the dialyser inlet and outlet lines immediately after HD started, hourly thereafter and just before the end of that HD session. For determination of free and total dabigatran in the dialyser fluid, dialysate samples were collected every 30 min during the HD on Day 3, with the first sample collected immediately after the start of dialysis.

For measurement of free and conjugated dabigatran blood samples were drawn into EDTA containing tubes, immediately placed in an ice/water bath (0-4°C) until centrifugation (at about 3,000 x g for 10 min, at 4°C) for plasma preparation. Plasma and dialysate samples were stored at -70°C until analysis. For pharmacodynamic analysis blood samples were collected into sodium citrate tubes, immediately placed in an ice/water bath (0-4°C) until centrifugation (at 2,500 x g for 20 min at 4°C) for plasma preparation. Plasma samples were stored at -20°C or below until analysis. When urine sampling was possible, a pre-dosing urine sample (2 ml aliquot, from urine collected over 24 h) was collected and throughout the study interval until Day 5. Citric acid was used to stabilise glucuronide conjugates. All aliquots were stored at –70°C.

Concentrations of non-conjugated, free dabigatran and of total dabigatran (sum of free dabigatran + dabigatran glucuronide) in plasma, urine and dialysate were analysed by validated high performance liquid chromatography tandem mass spectrometry methods at Nuvisan GmbH (Neu-Ulm, Germany), as described elsewhere (14).

## Pharmacokinetic and pharmacodynamic analysis

The primary pharmacokinetic objectives were the determination of dialysis clearance from blood ($CL_{bD}$) and plasma ($CL_D$), and the reduction of dabigatran plasma concentrations (%) during one 4 h dialysis session. To determine $CL_{bD}$ the concentrations in blood was calculated in a preceding step. As the distribution of active dabigatran from plasma into blood cells is negligible, the concentration of analyte in blood ($C_b$) was calculated according to equation: $C_b = C \times (1\text{-HTC})$, where C = concentration in plasma, $C_b$ = concentration in blood and HTC = hematocrit.

For each patient, $CL_{bD}$ was determined for the time points 51: 00 h, 52: 00 h, 53: 00 h and 54: 00 h during dialysis according the following equation: $CL_{bD} = (Q_{b,in} \times C_{b,in} - Q_{b,out} \times C_{b,out}) / C_{b,in}$, where $Q_{b,in}$ = blood flow of arterial blood entering the dialyser, $Q_{b,out}$ = blood flow of venous blood leaving the dialyser, $C_{b,in}$ = concentrations in the arterial blood entering the dialyser and $C_{b,out}$ = concentrations in the venous blood leaving the dialyser.

The arithmetic mean of $CL_{bD}$ determined at these four time points was then calculated for each patient and $CL_D$ was calculated according to the following equation: $CL_D = CL_{bD} \times C_{b,in}/C_{in}$, where $C_{in}$ = concentration in arterial plasma entering the dialyser.

The reduction of dabigatran plasma concentrations in percent ($C_{red}$) was calculated according to the equation: $C_{red} = (C_{start\ dialysis} - C_{end\ dialysis}) / C_{start\ dialysis} \times 100\%$, where $C_{start\ dialysis}$ = plasma concentration at the start of dialysis and $C_{end\ dialysis}$ = plasma concentration at the end of dialysis.

Secondary pharmacokinetic objectives were the calculation of pharmacokinetic parameters on Day 2 and Day 3 of treatment, including AUC of total dabigatran during the first 8 h after dosing ($AUC_{0-8}$), peak dabigatran concentration $C_{max}$, time to $C_{max}$ ($T_{max}$), renal clearance ($CL_R$) and amount of the drug excreted in dialysate ($Ae_{dialysate}$). The maximum redistribution in percent ($C_{redistr}$) was calculated according to the equation: $C_{redistri} = (C_{max\ after\ dialysis} - C_{end\ dialysis}) / C_{end\ dialysis} \times 100\%$, where $C_{max}$ after dialysis = maximum of the plasma concentration measured 4, 8 and 16 h after stop of dialysis.

The effect of dabigatran on blood coagulation was assessed by measurement of the aPTT and diluted thrombin time (dTT). Diluted thrombin time was determined using the commercially available Haemoclot® direct thrombin inhibitor assay (Hyphen BioMed, Neuville sur Oise, France). Prolongations of aPTT and dTT times are expressed relative to the baseline (pre-treatment) coagulation time. This assay was used in this study for measurement of thrombin-induced coagulation prolongation only but not for quantitative measurement of dabigatran plasma concentrations (21).

**Table 1: Concomitant medication of ESRD patients used in more than one participant.**

| Drugs | Number |
|---|---|
| Proton-pump inhibitors | 3 (43%) |
| Antihypertensive drugs | 7 (100%) |
| Calcium channel blockers | 2 (29%) |
| ACE inhibitors | 3 (43%) |
| β-adrenoreceptor antagonists | 4 (57%) |
| Vitamin D or vitamin D metabolites | 7 (100%) |
| Phosphate binding agents (oral) | 7 (100%) |
| Iron agents (i.v.) | 4 (100%) |
| Erythropoiesis-stimulating agents (i.v.) | 7 (100%) |

## Tolerability and safety assessments

Periodic safety assessments included physical examinations, vital signs (blood pressure, pulse rate), 12-lead ECGs, standard clinical laboratory evaluations (haematology, blood chemistry, urinalysis and coagulation parameters) as well as monitoring for adverse events (AEs), serious adverse events (SAEs), bleeding and overall tolerability. These assessments were performed periodically during the study and as part of the end-of-study evaluation.

## Statistical analysis

Pharmacokinetic parameters were determined using non-compartmental analysis, using WinNonlin Professional Network Ver-

sion 5.2 (Pharsight Corporation, Cary, NC, USA). All PK, PD, and safety endpoints were analysed using descriptive statistical methods. The relationship between PK parameters and coagulation parameters was assessed using regression models.

## Results

### Patient´s characteristics

Seven ESRD patients without atrial fibrillation were enrolled. All patients completed the study and all were included in all the pharmacokinetic, pharmacodynamic and safety evaluations. Study participants were male Caucasians with a mean age of 38.3 ± 10.9 years and mean BMI of 23.3 ± 2.3 kg/m$^2$. Underlying renal diseases were chronic glomerulonephritis (five patients), polycystic kidney disease and Fabry's Disease with renal involvement (one patient each). Medical histories of comorbidities were consistent with the diagnosis of ESRD and its secondary diseases (concomitant morbidities such as renal anaemia, secondary hyperparathyreoidism etc.). The concomitant medication is listed in ▶Table 1.

In Period 1, the target blood flow rate of 200 ml/min during the Day 3 HD session was achieved for all seven subjects. In Period 2, the maximal technically achieved blood flow rates during the Day 3 HD were in the range 350 to 395 ml/min (379 ± 10 ml/min), slightly lower than the targeted flow rate of 400 ml/min.

### Pharmacokinetics of dabigatran before dialysis

Pharmacokinetic parameters for total dabigatran for *Period 1 and 2* are summarised in ▶Table 2. Plasma concentration - time profiles were comparable between both Day 2 and 3 of each period and the first and second dosing period (▶Figure 2). The fraction of glucuronide conjugated dabigatran was on average 31% of total dabigatran. Renal clearance of total dabigatran was less than 1 ml/min ($CL_R$ 0.60 and 0.58 ml/min in Period 1 and 2, respectively) as calculated in those ESRD patients with residual urine production.

**Table 2: Pharmacokinetic parameters of total dabigatran after oral doses of dabigatran etexilate on Day 1 (150 mg), Day 2 (110 mg) and Day 3 (75 mg) (prior to haemodialysis) in treatment periods 1 and 2. Full plasma concentration-time profiles were assessed on Day 2 and Day 3.** *For tmax, median but no gCVs are shown. gCV, geometric coefficient of variation. range, min-max.

| | Day 2 | | | Day 3 | | |
|---|---|---|---|---|---|---|
| | gMean | gCV [%] | range | gMean | gCV [%] | range |
| **Treatment period 1 (n = 7)** | | | | | | |
| $C_{max}$, ng/ml | 194 | 53.1 | 103–439 | 176 | 54.1 | 99.6–398 |
| $t_{max}^*$, h | 4.00 | | 4.00–12.0 | 2.00 | | 1.00–2.00 |
| $AUC_{0-8}$, ng*h/ml | 1230 | 57.1 | 578–2760 | 1280 | 54.4 | 764–3020 |
| **Treatment period 2 (n = 7)** | | | | | | |
| $C_{max}$, ng/ml | 171 | 36.2 | 106–287 | 159 | 50.2 | 81.5–254 |
| $t_{max}^*$, h | 6.00 | | 2.00–12.0 | 2.00 | | 1.00–6.00 |
| $AUC_{0-8}$, ng*h/ml | 1140 | 39.4 | 697–1980 | 1180 | 50.2 | 587–1940 |

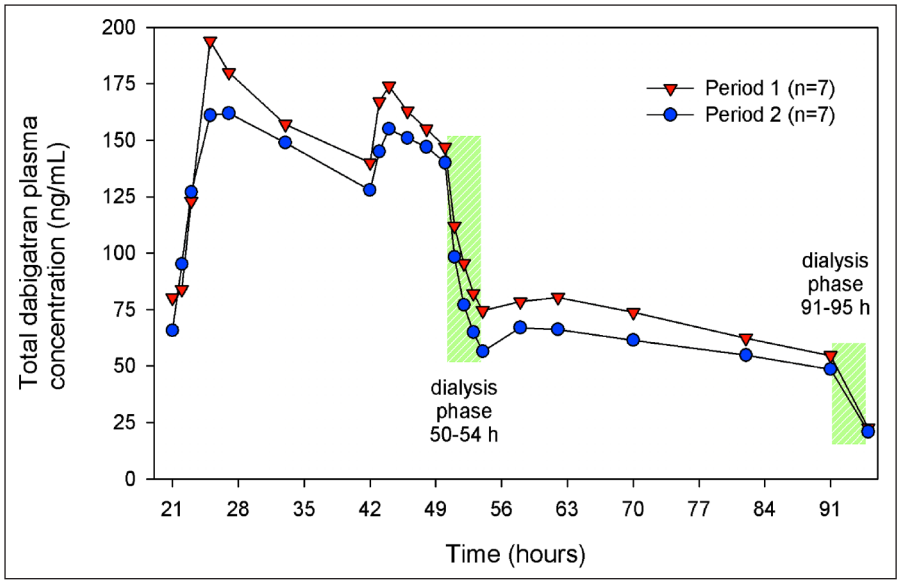



**Figure 2: Geometrical mean plasma concentration-time profiles of total dabigatran in both treatment periods.** Dabigatran was administered at 0, 21 and 42 h after the first dose; dialysis was performed from 50 to 54 and 91 to 95 h.

## Pharmacokinetics of dabigatran during haemodialysis

The effect of HD on the pharmacokinetic profile of total dabigatran is summarised in ►Table 3. HD of 4 h duration resulted in marked decreases in the dabigatran plasma concentrations from the start to the end of the dialysis session in both study periods (►Figure 2). The plasma fraction cleared from dabigatran reached a geometric mean (gMean) of 48.8% with a targeted blood flow of 200 ml/min and a gMean of 59.3% with 400 ml/min, respectively (►Table 3).

The inter-individual variability for dialysis clearance and for the fraction of dabigatran removed was very low (gCV<10%). The fraction of total dabigatran cleared from plasma in the "adapted" regular dialysis using a blood flow rate of 300 ml/min on Day 5 was (gMean) 58.5% (gCV 7. 5%) in *Period 1* and (gMean) 57.0% (gCV 2.8%) in *Period 2* (►Table 4).

## Pharmacokinetics of dabigatran after haemodialysis

After discontinuation of HD, gMean dabigatran plasma concentrations, measured 4, 8 and 16 h after stop of HD, redistributed slightly, i.e. the plasma concentration increased by 7.2% in *Period 1* and 15.5% in *Period 2* with high inter-individual variability (►Table 3). There was no obvious predictor of the redistribution effect.

## Pharmacodynamics

In both treatment periods, the pharmacodynamic time-effect profiles indicated that thrombin times and aPTTs increased after administration of DE. HD markedly reduced aPTT and dTT (►Table 5). The presence of low-dose heparin during dialysis on Day 3 did not influence dTT, but affected aPTT ratio´s as expected. The mean aPTT ratio during heparinisation increased from 1.81 ± 0.54 to 2.99 ± 1.17 in *Period* 1 and from 1.49 ± 0.431 to 2.97 ± 1.73 in *Period 2*.

| | Treatment period 1 targeted BFR [ml/min] 200 | | | Treatment period 2 targeted BFR [ml/min] 400 | | |
|---|---|---|---|---|---|---|
| | gMean | gCV [%] | range | gMean | gCV [%] | range |
| CLD,b [ml/min]* | 161 | 5.01 | 145–168 | 241 | 3.08 | 232–252 |
| CLD [ml/min]* | 120 | 5.09 | 110–127 | 183 | 4.03 | 170–194 |
| Plasma concentration, start of dialysis (50 h) [ng/ml] | 147 | 53.3 | 88.8–344 | 140 | 58.7 | 58.6–242 |
| Plasma concentration, end of dialysis (54 h) [ng/ml] | 74.6 | 44.0 | 52.1–165 | 56.5 | 58.2 | 25.8–101 |
| Fraction cleared from plasma [%] | 48.8 | 10.9 | 41.3–58.0 | 59.3 | 6.69 | 54.3–64.9 |
| Redistribution effect [%] | 7.52 | 146 | 1.95–21.9 | 15.5 | 121 | 2.17–35.3 |
| Extraction ratio [%] | 79.9 | 9.01 | 50.1–85.2 | 61.4 | 9.54 | 44.8–84.6 |
| Ae (dialysate) [µg] | 2260 | 48.1 | 1320–5260 | 2270 | 58.4 | 1100–4820 |

**Table 3: Geometric mean (gMean) pharmacokinetic parameters of total dabigatran for dialysis (Day 3) in period 1 (blood flow rate of 200 ml/min) and period 2 (blood flow rate approaching 400 ml/min).** *Calculated from dabigatran concentrations measured at dialyser inlet and outlet (please see method section). Ae (dialysate), amount excreted in dialysate; BFR, blood flow rate; range, min-max.

| Targeted blood flow rate (ml/min) | N | Percentage of total dabigatran cleared from plasma | | |
|---|---|---|---|---|
| | | gMean [%] | gCV [% of gMean] | range (min-max) |
| 200 (period 1, Day 3) | 7 | 48.8 | 10.9 | 41.3–58.0 |
| 300 (period 1, Day 5) | 7 | 58.5 | 6.36 | 52.6–63.5 |
| 300 (period 2, Day 5) | 7 | 57.0 | 2.76 | 55.0–59.1 |
| 400* (period 2, Day 3) | 7 | 59.3 | 6.69 | 54.3–64.9 |
| Results of the two sided paired t-test:Difference experimental dialysis BFR200 – BFR400: mean:–10.3586, 95% CIfrom–15.9948to–4.7223; Difference within period 1BFR200 – BFR300: mean:–9.5157,95% CI from–12.9017to–6.1297; Difference within period 2BFR300 – BFR400: mean:–2.3629,95% CIfrom –6.6967to1.9709. | | | | |

**Table 4: Effect of dialysis blood flow rate on fraction of dabigatran cleared from plasma.** * Actual maximum blood flow rates ranged from 365 to 395 ml/min.

### Pharmacokinetic – pharmacodynamic evaluation

The relationship between plasma concentrations of dabigatran and tests that can evaluate the anticoagulant activity of dabigatran were evaluated using a linear least-squares regression analysis. A linear relationship between dabigatran plasma concentration and anticoagulant activity for both dTT and aPTT could be demonstrated. Dialysis did not affect the linear relationship of dabigatran on dTT (►Figure 3) whereas the effect on aPTT was masked by heparin administration during dialysis (not shown).

### Safety and tolerability of dabigatran

In both treatment periods, all seven subjects received all three scheduled doses of DE. No deaths, SAEs, other significant AEs, or AEs of severe intensity were observed. Over the course of the trial, AEs were reported in two subjects, with only one AE (mild epistaxis), which was treatment-related. The other AEs reported (mild headache and nasopharyngitis) were not considered treatment-related. The three reported AEs resolved spontaneously without any intervention. No changes of standard safety laboratory values were of relevance or reported as an AE by the investigator. There were no notable abnormalities for vital signs or ECG measurements.

## Discussion

Dabigatran has been investigated for the prevention and treatment of both arterial and venous thromboembolic diseases. DE, 150 mg twice daily has been proven to be superior to warfarin (target INR 2.0 – 3.0) for preventing a composite endpoint of stroke (ischaemic and haemorrhagic) and systemic embolism in patients with non-valvular AF and at least one risk factor for stroke (10). Dabigatran also has proven safety and efficacy for the prevention of venous thromboembolic events in patients undergoing major orthopaedic surgery and for the treatment and secondary prevention of deep-vein thrombosis and pulmonary emboli. Given the increasing clinical use of DE, there is need for a fast, simple and reliable method to reverse its anticoagulant activity (22). The potential of HD to fulfill this need was evaluated in this study.

**Table 5: Effect of haemodialysis (Day 3) on diluted thrombin time (dTT = anti-FIIa) ratio and aPTT ratio (ratios calculated relative to pre-treatment values).**
*Measured 50 h after first dose; †measured 54 h after first dose. gMean, geometric mean; gCV, geometric coefficient of variation; range, min-max.

| | Before dialysis* | | | After dialysis† | | |
|---|---|---|---|---|---|---|
| | gMean | gCV [%] | range | gMean | gCV [%] | range |
| **dTT ratio** | | | | | | |
| Treatment period 1 | 1.69 | 20.9 | 1.31–2.34 | 1.25 | 16.8 | 0.94–1.56 |
| Treatment period 2 | 1.78 | 24.4 | 1.27–2.43 | 1.24 | 16.7 | 0.899–1.43 |
| **aPTT ratio** | | | | | | |
| Treatment period 1 | 1.75 | 26.3 | 1.34–2.96 | 1.27 | 5.55 | 1.17–1.37 |
| Treatment period 2 | 1.44 | 27.3 | 1.08–2.32 | 1.27 | 19.9 | 0.875–1.49 |

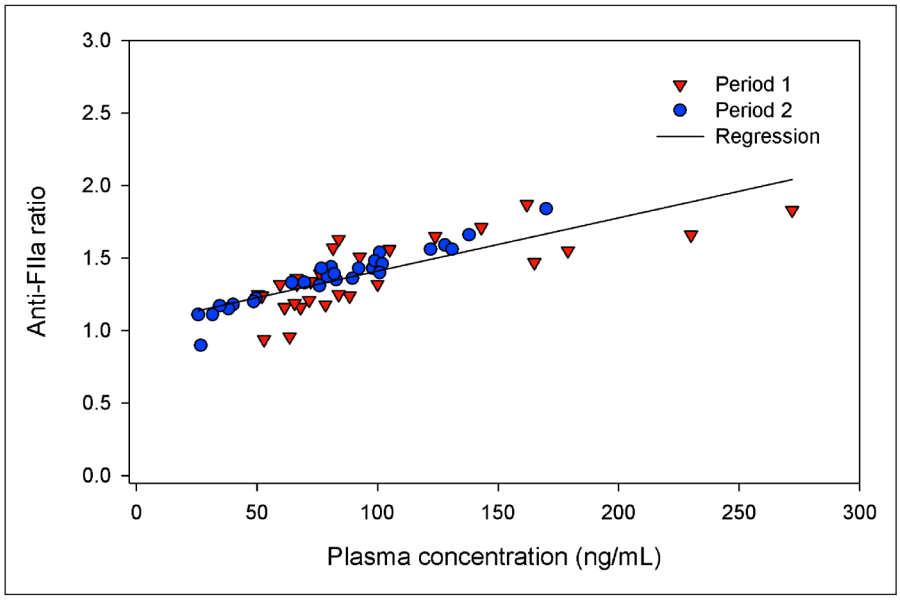



**Figure 3: Relationship between dTT ratio and plasma concentration of total dabigatran during Day 3 dialysis (51–54 h after first dose) in both treatment periods.**
Squares indicate data from period 1 and circles from period 2.

The present study delivered four key results: 1) in ESRD patients, a specific dosing regimen (150 mg on Day 1, 110 mg on Day 2 and 75 mg on Day 3) yielded peak dabigatran plasma concentrations on Day 3 comparable to those observed in AF patients with atrial fibrillation in RE-LY dosed with 150 mg b.i.d.; however, it should be noted that the selected dose regimen is not considered a suitable treatment regimen for ESRD patients undergoing regular HD and who are in need of regular anticoagulant therapy due to comorbidities 2) a 4 h optimised HD session with actual blood flow rate of 200 ml/min removed 48.8% of dabigatran concentration from plasma volume (central compartment) and 59.3% with blood flow rates of 350-395 ml/min, respectively; 3) the anticoagulant activity of dabigatran was reduced proportionally to the HD-related reduction in plasma levels; 4) following dialysis, there was minor redistribution of dabigatran into the plasma compartment (described as 7.5-15.5% increase in plasma concentration after end of HD).

There were several reasons for choosing ESRD patient for this study. First, renal excretion of dabigatran is negligible in ESRD patients with little or no urine production. Thus, renal clearance does not interfere with an analysis of the maximal possible elimination of dabigatran by HD. Second, the bleeding risk at the arteriovenous shunt puncture side is far lower compared to the risk with placing a central HD catheter. Third, using the ESRD patient´s arteriovenous fistula allowed the evaluation of a broader range of blood flow rates during HD. Fourth, the dialysis procedure itself did not add any extra burden or risk for this study population. Therefore, ESRD patients represent an excellent human model to evaluate the effect of HD on the dabigatran exposure.

The dosing regimen for DE (150 mg, 110 mg and 75 mg each subsequent day) yielded systemic peak drug exposures (Cmax) on Day 3 that were similar to those reported at steady state in AF patients receiving DE 150 mg twice daily in RE-LY (gMean 2 h post-dose concentration after 150 mg b.i.d. in RE-LY = 175 ng/ml [gCV = 74.1%) (N = 4598)] (4, 15, 20).

In another study with ESRD patients, a single, oral dose of 50 mg DE was administered to ESRD subjects at the start of a 4 h HD session to explore the potential of dialysis to remove dabigatran (14). The investigator reported excretion ratios (i.e. comparing pre- to post dialysis filter concentrations) were in the range of 62% to 68%. However, the actual fraction of dabigatran cleared from plasma was not shown. In the present study, ESRD patients were exposed to multiple DE doses selected to result in peak plasma concentrations comparable to AF patients receiving dabigatran etexilate 150 mg b.i.d. with creatinine clearances above 30 ml/min and as such clinically relevant to assess the effects of HD on dabigatran removal and redistribution. Under these conditions, we found that a 4 h dialysis session reduced dabigatran plasma concentrations (fraction cleared from plasma) by 48.8% when the targeted blood flow was 200 ml/min and 59.3% at 400 ml/min, respectively. The corresponding $CL_D$ were (gMean) 120 and 183 ml/min, respectively, indicating that total dabigatran clearance from plasma is amplified with increase of the blood flow, however this effect is not linear. As $CL_D$ is only dependent on flow rates and physicochemical properties of the membrane, expressed as KoA (23), but not concentration dependent without any saturation issues, it can be expected to achieve similar results in non ESRD patients and patients being overdosed.

In our study design, three doses of DE were administered 50, 29, and 8 h prior to dialysis. This multiple dose regimen should have permitted adequate distribution of dabigatran into the peripheral compartment before the start of HD to assess the order of magnitude of a potential redistribution of dabigatran from e.g. the interstitial fluid into plasma. The nearly congruent PK time curves on Day 2 and 3 (e.g. first 8 h post dosing) support that the desired distribution of dabigatran into the interstitial fluid occurred as expected. Following dialysis a relatively small redistribution effect (<16%) into the central compartment (plasma/blood) was observed. Redistribution reached its maximum 4.0 to 8.1 h after the end of dialysis. As the maximum redistribution is calculated based on the lower plasma level at the end of the dialysis and no fast increase was observed the typical value should be of minor clinical relevance. Some uncertainty remains with respect to the high variability in the redistribution. There might be situations of acute bleeding in combination with individually higher redistribution which could be clinically relevant. Based on the available data no final assessment can be made if this magnitude of redistribution might change once extreme (e.g. accidental or suicidal) supra-

### What is known about this topic?

- Dabigatran is widely used for thrombosis prophylaxis, also in long-term indications such as stroke prevention in patients with atrial fibrillation.
- Dabigatran has no specific antidote. With unspecific reversal agents like fresh frozen plasma or factor concentrates (e.g. PCC) no broad clinical experience is available. However, some clinical setting may require a rapid reversal of dabigatran's activity (include major bleeding, the need for emergency surgery, acute kidney injury and overdosing).
- The drug has a half-life of 12–17 hours and eliminated via renal excretion, assuming that the accumulation is unlikely. Dabigatran has low plasma protein binding, is highly water soluble and has an apparent volume of distribution of approx. 60-70 litre and can, thus, be removed by haemodialysis.

### What does this paper add?

- Dabigatran plasma levels similar to those in effectively treated AF patients can be decreased by at least half by a 4 hour haemodialysis procedure.
- A 4 hour optimised haemodialysis session with actual blood flow rate of 200 and 350-395 ml/minute removed 48.8% and 59.3% of dabigatran concentration from plasma volume, respectively.
- The anticoagulant activity of dabigatran was reduced proportionally to the haemodialysis-related reduction in plasma levels;
- There was minor redistribution of dabigatran into the plasma compartment after dialysis (described as 7.5-15.5% increase in plasma concentration after end of haemodialysis).

therapeutic plasma concentrations are present after multiple dosing.

In both treatment periods, pharmacodynamic assessment indicated that aPTT and dTT increased after administration of DE, and that dialysis substantially lowered aPTT and dTT ratios. Effects were similar in both treatment periods. The relationship between dabigatran plasma concentrations and aPTT and dTT values was the same as has been seen in all other patient and subject populations that have been studied (12, 13). The presence of low-dose heparin during dialysis did not affect the dTT values, but the aPTT values were elevated as expected, precluding definitive interpretation of changes in aPTT ratio in the dialysis setting. Therefore, the data suggest that dTT coagulation is suitable to measure dabigatran related anticoagulant activity even during HD.

In this study, the selected DE regimen was well tolerated. Only one minor drug-related AE was reported (mild transient epistaxis). Due to the low number of patients no final assessment about the safety profile of dabigatran in ESRD patients can be made.

In both the catheter and shunt dialysis settings that were evaluated, a low-dose heparin anticoagulation scheme was used to ensure effective HD (1,000 IU heparin bolus followed by 500 IU/h). The amount of heparin used according to this anticoagulation scheme was less than commonly used in usual HD settings. The adverse event data did not suggest an increased bleeding rate for the patients enrolled into the present trial and exposed to dabigatran concentrations (similar to those observed in AF patients) plus continuous low-dose administration of heparin. However, no firm conclusion can be drawn how this beneficial risk benefit profile might change if low-dose heparin might be applied in a HD setting to a patient who might be exposed to supra-therapeutic plasma levels of dabigatran.

The data collected in the trial could have relevance in an additional clinical context. As outlined in ►Table 4 the data suggest that the percentage of total dabigatran cleared from plasma does not increase linearly with an increase of the blood flow rate during HD. This observation might have important clinical implications with regard to decision making which blood flow rate may be applicable in a potentially critical clinical situation.

Our investigation has some limitations. First, the number of study subjects was relatively small leading to an analysis that is based on a total of 28 HD sessions. Secondly, study subjects were all male Caucasians. However, there is no evidence that pharmacokinetics of dabigatran is meaningfully influenced by ethnicity and the influence by gender adjusted for renal function is limited. Furthermore, since the dialysis clearance is mainly due to certain physicochemical properties of the dialysis filter, and protein binding of the studied drug, it seems justified to expect our observed results would be similar to those if women, patients of other ethnicities and importantly to patients with the target indication AF were studied. Thirdly, the study population consisted of clinical stable patients with relatively few comorbidities other than their ESRD and its expected consequences. Thus, the therapeutic benefit of dialysis still requires confirmation in patients with bleeding complications or other emergency situations.

In this regard one case report has been recently published indicating that emergency HD was clinically effective in decreasing bleeding as well as in the removal of dabigatran from the body (24) and a second case report described the useful application of HD for dabigatran removal before cardiac surgery (25).

## Conclusions

The present study demonstrated dabigatran plasma levels similar to those in effectively treated AF patients can be decreased by at least half by a 4 h optimised HD procedure. Reductions in dabigatran plasma concentrations were associated with a comparable reduction of the anticoagulant activity of dabigatran.

### Conflicts of interest

The trial was funded by Boehringer Ingelheim. This research was conducted at Charité Research Organisation and Department of Nephrology, Charité, Berlin, Germany. Stephan Formella, Viktoria Moschetti, Karl-Heinz Liesenfeld, Thorsten Lehr, Sebastian Härtter, Jeffrey Friedman and Andreas Clemens are employee of Boehringer Ingelheim. None of the other authors declares any conflict of interest.

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