Effective removal of dabigatran by idarucizumab or hemodialysis – a physiologically based pharmacokinetic modeling analysis

Supplementary information

Laura Maria Fuhr¹, Nina Hanke¹, Bernd Meibohm², Thorsten Lehr¹

¹ Clinical Pharmacy, Saarland University, Saarbruecken, Germany
² Department of Pharmaceutical Sciences, College of Pharmacy, The University of Tennessee Health Science Center, Memphis, Tennessee, USA

Corresponding Author:
Prof. Dr. Thorsten Lehr
Saarland University, Clinical Pharmacy
Campus C2 2, 66123 Saarbruecken
Phone: +49 681 302 70255, Fax: +49 681 302 70258
thorsten.lehr@mx.uni-saarland.de
Thorsten Lehr: orcid.org/0000-0002-8372-1465

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1 Methods

1.1 Clinical study data

All clinical study data that were available for the development of the dabigatran hemodialysis model are presented in Table S1.

### Table S1 Clinical study data of dabigatran hemodialysis

| Dose       | Route           | n  | Women [%] | Age (SD) [years] | Weight (SD) [kg] | BFR [mL/min] | DFR [mL/min] | Dialysis duration [h] | CrCl [mL/min] | Reference       |
|------------|-----------------|----|-----------|------------------|------------------|--------------|--------------|------------------------|---------------|-------------------|
| 150/110/75 | po, capsule     | 7  | 0         | 38 (10.9)        | 74 (9.0)         | 200          | 700          | 4                      | 11            | Khadzhynov 2013 [1] |
| 150        | po, capsule (bid)| 1  | 0         | 79               | 80               | 320          | 700          | 6                      | 36            | Warkentin 2012 [2]  |
| 150        | po, capsule (bid)| 1  | 0         | 94               | n.g.             | 350          | n.g.         | 3                      | 79            | Chang 2013 [3]     |
| 150/110/75 | po, capsule     | 7  | 0         | 38 (10.9)        | 74 (9.0)         | 400          | 700          | 4                      | 11            | Khadzhynov 2013 [1] |

BFR: blood flow rate, bid: twice a day, CrCl: creatinine clearance, DFR: dialysate flow rate, n.g.: not given, po: orally, SD: standard deviation
1.2 Calculation of plasma concentrations and fractions excreted to urine

1.2.1 Idarucizumab

When determining idarucizumab plasma concentrations and fractions excreted to urine in clinical studies, the assays did not distinguish between free idarucizumab and dabigatran (glucuronide) bound idarucizumab.

Since idarucizumab and the idarucizumab-dabigatran (glucuronide) complexes are represented in the model as different molecules, the measured plasma concentrations were calculated in the model as “sum idarucizumab” and fractions excreted to urine were calculated as “fraction excreted of sum idarucizumab”, consisting of idarucizumab itself, the idarucizumab-dabigatran complexes and the idarucizumab-dabigatran glucuronide complexes, which were calculated in the model by Equations (1) and (2).

\[ \text{IDA}_{\text{sum}} \ [\mu\text{mol/L}] = [\text{IDA}] \ [\mu\text{mol}] \cdot + [\text{IDA-}\text{DAB}] \ [\mu\text{mol}] + [\text{IDA-}\text{DABG}] \ [\mu\text{mol}] \]  

(1)

with \( \text{IDA}_{\text{sum}} = \) sum idarucizumab plasma concentration, \([\text{IDA}] = \) idarucizumab plasma concentration, \([\text{IDA-}\text{DAB}] = \) idarucizumab-dabigatran complex plasma concentration and \([\text{IDA-}\text{DABG}] = \) idarucizumab-dabigatran glucuronide complex plasma concentration.

\[ \text{fe}_{\text{IDA}_{\text{sum}}} = \frac{\text{IDA} \ [\mu\text{mol}] + \text{IDA-}\text{DAB} \ [\mu\text{mol}] + \text{IDA-}\text{DABG} \ [\mu\text{mol}]}{\text{IDA}_{\text{dose}} \ [\mu\text{mol}]} \]  

(2)

with \( \text{fe}_{\text{IDA}_{\text{sum}}} = \) fraction excreted of sum idarucizumab, \([\text{IDA}], [\text{IDA-}\text{DAB}] \text{ and } [\text{IDA-}\text{DABG}] = \) molar amounts of idarucizumab, idarucizumab-dabigatran complex and idarucizumab-dabigatran glucuronide complex, respectively, that were excreted with the urine and \( \text{IDA}_{\text{dose}} = \) molar amount of idarucizumab administered.
1.2.2 Dabigatran

Dabigatran plasma concentrations were determined as pharmacologically active dabigatran, consisting of dabigatran and dabigatran glucuronide not bound to plasma proteins or idarucizumab. In the assays, plasma samples were hydrolyzed to remove the glucuronide-conjugation and idarucizumab as well as plasma proteins were removed during plasma ultrafiltration [4]. Plasma concentrations were calculated in the model as “unbound sum dabigatran” according to Equation (3).

\[
\text{DAB}_{\text{unb sum}} [\mu\text{mol/L}] = [\text{DAB}] [\mu\text{mol/L}] \cdot f_u \text{DAB} + [\text{DABG}] [\mu\text{mol/L}] \cdot f_u \text{DABG}
\]  

(3)

with \( \text{DAB}_{\text{unb sum}} \) = unbound sum dabigatran plasma concentration, \([\text{DAB}]\) = dabigatran plasma concentration and \([\text{DABG}]\) = dabigatran glucuronide plasma concentration in g/L and \( f_u \) = fraction unbound to plasma proteins, which was assumed to be the same for dabigatran and its glucuronide.

Fractions excreted to urine were determined in clinical studies as “fraction excreted of unconjugated dabigatran”, which reflects the amount of dabigatran in urine as fraction of the administered dabigatran etexilate dose. Urine samples were analyzed without ultrafiltration [4]. Therefore, idarucizumab bound dabigatran was also determined. The fraction excreted to urine was calculated in the model according to Equation (4).

\[
\text{fe}_{\text{unconj DAB}} = \frac{[\text{DAB}] + \text{IDA-DAB}}{\text{DE}_{\text{dose}}} [\mu\text{mol}]
\]

(4)

with \( \text{fe}_{\text{unconj DAB}} \) = fraction excreted of unconjugated dabigatran, \([\text{DAB}]\) and \([\text{IDA-DAB}]\) = molar amounts of dabigatran and idarucizumab-dabigatran complex excreted with the urine and \( \text{DE}_{\text{dose}} \) = molar amount of dabigatran etexilate administered.
1.3 Extension of the kidney compartment

To describe the renal reabsorption of idarucizumab, the default kidney compartment of PK-Sim was extended by addition of a proximal tubule compartment in MoBi®, as described previously by Balazki et al [5]. The glomerular filtration of molecules from the blood into the renal tubule is described by the glomerular filtration rate, according to Equation (5):

\[
GFR = c_{\text{p, kidney}} \cdot \text{GFR}_{\text{spec}} \cdot m_{\text{kidney}}
\]  

with GFR = glomerular filtration rate of the molecule, \(c_{\text{p, kidney}}\) = plasma concentration of the molecule in the kidney, \(\text{GFR}_{\text{spec}}\) = glomerular filtration rate of the individual normalized to kidney weight (266 mL/min/kg kidney for healthy individuals), and \(m_{\text{kidney}}\) = kidney weight.

Physiologically, 60% of the filtered water is reabsorbed along the tubule. Therefore, the flow from the tubule into the urine compartment can be described by a filtrate flow rate that is reduced to 40% of the flow from the glomerulus into the renal tubule [5]:

\[
Q = \text{GFR}_{\text{spec}} \cdot m_{\text{kidney}} \cdot 0.4
\]  

\[
\text{FlowIntoUrine} = c_{\text{p, kidney}} \cdot Q
\]  

with \(Q\) = filtrate flow rate, \(\text{GFR}_{\text{spec}}\) = glomerular filtration rate of the individual normalized to kidney weight, \(m_{\text{kidney}}\) = kidney weight and \(c_{\text{p, kidney}}\) = plasma concentration of the molecule in the kidney.

For the implementation of megalin mediated renal reabsorption and subsequent endosomal degradation of idarucizumab, an endosomal compartment was added into the intracellular subcompartment of the kidney. The volume of this endosomal compartment was calculated according to Equation (8), assuming a volume that comprises 20% of the volume of the kidney cells. This value is based on the assumptions of Garg et al. for the ratio of endosomal volume to endothelial cell volume [6], which is the default used in the PK-Sim® protein model.

\[
V_{\text{kidney,endo}} = V_{\text{kidney,cell}} \cdot f_{\text{endo}}
\]  

with \(V_{\text{kidney,endo}}\) = volume of the endosomal subcompartment of the kidney, \(V_{\text{kidney,cell}}\) = volume of the intracellular subcompartment of the kidney and \(f_{\text{endo}}\) = endosomal fraction of 0.2.

Parameterization of the final tubule compartment is shown in Table S3.
The transport of idarucizumab from tubule lumen into the endosomal compartment by megalin was described using Michaelis-Menten kinetics:

\[ v_0 = \frac{k_{\text{cat}} \cdot [M] \cdot [\text{IDA}]}{K_m + [\text{IDA}]} \tag{9} \]

with \( v_0 \) = reaction rate, \( k_{\text{cat}} \) = catalytic rate constant describing the maximum megalin turnover per time, \([M]\) = megalin concentration, \([\text{IDA}]\) = idarucizumab concentration and \(K_m\) = idarucizumab concentration needed to reach half of \(k_{\text{cat}} \cdot [M] = V_{\text{max}}\).

Analyzing the urinary excretion of idarucizumab in elderly and renally impaired individuals, a correlation between individually optimized megalin \(k_{\text{cat}}\) and reported CrCl could be demonstrated (Fig. S1, Table S2). This identified correlation was incorporated into the model using an \(E_{\text{max}}\) function:

\[ k_{\text{cat}} = \frac{k_{\text{cat, max}} \cdot \text{GFR}^{n}_{\text{IND}}}{\text{GFR} \times 50^{n} + \text{GFR}^{n}_{\text{IND}}} \tag{10} \]

with \(k_{\text{cat}}\) = megalin catalytic rate constant, \(k_{\text{cat, max}}\) = maximum megalin catalytic rate constant, \(\text{GFR}^{n}_{\text{IND}}\) = glomerular filtration rate of the respective individual, \(\text{GFR} 50 = \) glomerular filtration rate needed to reach half of megalin \(k_{\text{cat, max}}\) and \(n\) = Hill factor. The parameters of the \(E_{\text{max}}\) model were optimized.

The transport of idarucizumab from the renal tubule into the kidney endosome is followed by endosomal degradation, which was introduced into the kidney endosome compartment with the default equation used in PK-Sim® [7]:

\[ \frac{dN}{dt} = CL_{\text{spec}} \cdot C_{\text{endo}} \cdot V_{\text{endo}} \tag{11} \]

with \(CL_{\text{spec}}\) = specific endosomal clearance, \(C_{\text{endo}} = \) endosomal concentration of idarucizumab and \(V_{\text{endo}} = \) volume of the endosome compartment.
Fig. S1 Megalin $k_{\text{cat}}$, describing the idarucizumab reuptake from the renal tubule lumen into the kidney intracellular endosome, as a function of glomerular filtration rate. Blue circles illustrate the optimized $k_{\text{cat}}$ values of each mean individual versus its corresponding reported glomerular filtration rates. The solid line presents the derived $E_{\text{max}}$ function which was implemented into the model to describe megalin $k_{\text{cat}}$ in dependence of GFR. GFR: glomerular filtration rate, $k_{\text{cat}}$: catalytic rate constant

Table S2 Correlation of optimized megalin $k_{\text{cat}}$ with the glomerular filtration rate reported in the study protocol

| Study            | IDA dose [mg] | DE dose [mg] | Reported GFR [mg/mL] | Optimized $k_{\text{cat}}$ [1/min] | $E_{\text{max}}$ model $k_{\text{cat}}$ [1/min] |
|------------------|--------------|--------------|----------------------|-------------------------------------|-----------------------------------------------|
| Glund 2016 [8]   | 2500         | 150          | 58.7                 | 0.0197                              | 0.0204                                        |
| Glund 2016 [8]   | 5000         | 150          | 72.8                 | 0.0306                              | 0.0247                                        |
| Glund 2016 [8]   | 1000         | 150          | 79.9                 | 0.0214                              | 0.0266                                        |
| Glund 2016 [8]   | 5000         | 220          | 83.3                 | 0.0251                              | 0.0274                                        |
| Glund 2016 [8]   | 1000         | 220          | 84.8                 | 0.0285                              | 0.0278                                        |
| Glund 2016 [8]   | 2500         | 220          | 97.5                 | 0.0281                              | 0.0306                                        |
| Glund 2016 [8]   | 5000         | 220          | 110.4                | 0.0422                              | 0.0329                                        |
| Yasaka 2017 [9]  | 1000         | 220          | 121.0$^a$            | 0.0343                              | 0.0360                                        |
| Yasaka 2017 [9]  | 2000         | 220          | 121.0$^a$            | 0.0422                              | 0.0360                                        |
| Yasaka 2017 [9]  | 4000         | 220          | 121.0$^a$            | 0.0317                              | 0.0360                                        |
| Yasaka 2017 [9]  | 2500 + 2500  | 220          | 121.0$^a$            | 0.0227                              | 0.0345                                        |
| Yasaka 2017 [9]  | 1000         | -            | 121.0$^a$            | 0.0231                              | 0.0345                                        |
| Yasaka 2017 [9]  | 2000         | -            | 121.0$^a$            | 0.0182                              | 0.0345                                        |
| Yasaka 2017 [9]  | 4000         | -            | 121.0$^a$            | 0.0237                              | 0.0345                                        |
| Yasaka 2017 [9]  | 8000         | -            | 121.0$^a$            | 0.0391                              | 0.0345                                        |
| Glund 2015 [10]  | 4000         | 220          | 121.6                | 0.0465                              | 0.0345                                        |
| Glund 2015 [11]  | 1000         | -            | 132.0$^a$            | 0.0545                              | 0.0345                                        |
| Glund 2015 [11]  | 2000         | -            | 132.0$^a$            | 0.0472                              | 0.0345                                        |
| Glund 2015 [11]  | 4000         | -            | 132.0$^a$            | 0.0388                              | 0.0368                                        |
| Glund 2015 [10]  | 5000 + 2500  | 220          | 135.2                | 0.0315                              | 0.0367                                        |
| Glund 2015 [10]  | 2000         | 220          | 137.9                | 0.0296                              | 0.0346                                        |
| Glund 2015 [10]  | 1000         | 220          | 138.8                | 0.0402                              | 0.0364                                        |

$^a$ mean CrCl of the whole clinical trial was used, since no CrCl for the different treatment arms were given.

DE: dabigatran etexilate, GFR: glomerular filtration rate, IDA: idarucizumab, $k_{\text{cat}}$: catalytic rate constant
Given that idarucizumab (MW = 47,500 g/mol) is much larger than dabigatran (MW = 472 g/mol) or its glucuronide (MW = 647 g/mol) we assumed that the pharmacokinetics of the idarucizumab-dabigatran and idarucizumab-dabigatran glucuronide complexes do not differ from those of idarucizumab itself. Therefore, endosomal uptake and degradation in the kidney was also enabled for the complexes. To correctly capture the saturation of megalin in the presence of idarucizumab and complexes, the three molecules were implemented as competitive inhibitors of each other’s transport. Competitive inhibition of megalin is incorporated according to the following equation (exemplarily described for idarucizumab transport by megalin):

\[ K_{m, IDA}^{app} = K_{m, IDA} \cdot \left(1 + \frac{[IDA-DAB]}{K_i, IDA-DAB} + \frac{[IDA-DABG]}{K_i, IDA-DABG}\right) \]  \hspace{1cm} (12)

with \( K_m = \) Michaelis-Menten constant, \( K_{m, IDA}^{app} = \) apparent \( K_m \), \([IDA-DAB] = \) idarucizumab-dabigatran complex concentration, \([IDA-DABG] = \) idarucizumab-dabigatran glucuronide complex concentration and \( K_i = \) dissociation constant of the inhibitor, which is assumed to be equal to its megalin \( K_m \).

After breakdown of the complexes in the kidney endosome, dabigatran and its glucuronide are released back into the tubule and excreted with the urine. This return to the renal tubule is modeled as exocytotic process according to the following equation:

\[ \frac{dN}{dt} = k_{rec} \cdot C_{endo} \cdot V_{endo} \] \hspace{1cm} (13)

with \( k_{rec} = \) rate constant for exocytosis of dabigatran or dabigatran glucuronide, \( C_{endo} = \) dabigatran or dabigatran glucuronide concentration in the kidney endosome compartment and \( V_{endo} = \) volume of the kidney endosome compartment. \( k_{rec} \) was identified during parameter identification.

**Table S3** Parameterization of the renal tubule compartment

| Parameter  | Unit | Value used in simulation | Literature value | Reference | Description |
|------------|------|--------------------------|------------------|-----------|-------------|
| \( V_{tubule} \) | L    | 0.08                     | 0.08             | [5]       | Volume of proximal tubule compartment |
| \( Q \)    | L/min| 0.05                     | 0.05             | [5]       | Filtrate flow rate from proximal tubule to the urine |
| \( V_{endo} \) | L    | 0.04                     | 0.04             | [6]       | Volume of the endosomal compartment in the intracellular space of the kidney |
| \( k_{rec} \) | 1/h  | 1.2                      | -                | -         | Rate constant for tubular recycling |
1.4 Interaction modeling

The interaction of idarucizumab with dabigatran and dabigatran glucuronide occurs with a stoichiometric ratio of 1:1 [12] and was described according to:

\[ \text{[IDA]} + \text{[DAB]} \rightleftharpoons \text{[IDA-DAB]} \]

\[ K_d = \frac{k_{\text{off}}}{k_{\text{on}}} = \frac{[\text{IDA}] \cdot [\text{DAB}]}{[\text{IDA-DAB}]} \]  

(14)

\[ \text{[IDA]} + \text{[DABG]} \rightleftharpoons \text{[IDA-DABG]} \]

\[ K_d = \frac{k_{\text{off}}}{k_{\text{on}}} = \frac{[\text{IDA}] \cdot [\text{DABG}]}{[\text{IDA-DABG}]} \]  

(15)

with [IDA] = idarucizumab concentration, [DAB] = dabigatran concentration, [IDA-DAB] = idarucizumab-dabigatran complex concentration, [DABG] = dabigatran glucuronide concentration, [IDA-DABG] = idarucizumab-dabigatran glucuronide complex concentration, \( K_d \) = dissociation constant, \( k_{\text{off}} \) = dissociation rate constant, \( k_{\text{on}} \) = association rate constant.

1.5 Pharmacodynamic modeling

The impact of dabigatran on the coagulation markers aPTT, dTT, ECT and TT was described according to the following empirically derived equations, similar to the approach of Liesenfeld et al. [13]:

\[ \text{aPTT} = 17.94 \cdot \frac{[\text{DAB}]}{0.04 + [\text{DAB}]} + 61.67 \cdot [\text{DAB}] + 30.21 \]  

(16)

\[ \text{dTT} = 88.30 \cdot [\text{DAB}] + 31.59 \]  

(17)

\[ \text{ECT} = 209.70 \cdot [\text{DAB}] + 34.85 \]  

(18)

\[ \text{TT} = 106.28 \cdot \frac{[\text{DAB}]}{0.19 + [\text{DAB}]} + 144.02 \cdot [\text{DAB}] + 12.93 \]  

(19)

with aPTT = activated partial thromboplastin time, dTT = dilute thrombin time, ECT = ecarin clotting time, TT = thrombin time and [DAB] = unbound sum dabigatran plasma concentrations.
1.6 Model evaluation

1.6.1 Calculation of MRD and GMFE

MRDs of the predicted plasma concentrations were calculated according to:

\[
MRD = 10^x; \quad x = \sqrt[20]{\frac{\sum \left(\log_{10}(c_{\text{observed}}) - \log_{10}(c_{\text{predicted}})\right)^2}{n}}
\]

with \( MRD = \text{mean relative deviation}, \ c_{\text{observed}} = \text{observed plasma concentration}, \ c_{\text{predicted}} = \text{corresponding predicted plasma concentration} \) and \( n = \text{number of observed values} \). An MRD value < 2 signifies that the average of the plasma concentrations predicted by the model equals the observed values or deviates not more than twofold, characterizing an adequate prediction [14].

GMFEs of the \( \text{AUC}_{0-\infty} \) values of the predicted plasma concentration-time profiles were calculated according to:

\[
\text{GMFE} = 10^x; \quad x = \left( \frac{\sum |\log_{10}\left(\text{AUC}_{0-\infty, \text{predicted}}/\text{AUC}_{0-\infty, \text{observed}}\right)|}{n} \right)
\]

with \( \text{GMFE} = \text{geometric mean fold error}, \ \text{AUC}_{0-\infty, \text{observed}} = \text{observed area under the plasma concentration-time curve from time point 0 to infinity}, \ \text{AUC}_{0-\infty, \text{predicted}} = \text{corresponding predicted area under the plasma concentration-time curve} \) and \( n = \text{number of studies} \). A GMFE value < 2 characterizes an adequate prediction.
1.6.2 Sensitivity analysis

A sensitivity analysis was performed with the final PBPK model of idarucizumab, to investigate the impact of single model parameters on the predicted \( \text{AUC}_{0-\infty} \) following application of 5000 mg idarucizumab as bolus injection. Parameters were included in the analysis if they have been optimized \((K_m, k_{\text{cat}}, \text{GFR fraction}, \text{solute radius})\) or if they are associated with optimized parameters \((\text{megalin reference concentration}, \text{GFR}_{50}, k_{\text{cat,max}}, n, \text{individual GFR})\). 1000\% perturbation range and 9 variation steps were used for the sensitivity analysis.

Sensitivity to a parameter is calculated as the ratio of the relative change of the simulated AUC to the relative variation of the parameter around the value used in the final model according to Equation (22):

\[
S = \frac{\Delta \text{AUC}}{\text{AUC}} \cdot \frac{p}{\Delta p}
\]

with \(S\) = sensitivity of the AUC to the examined model parameter, \(\Delta \text{AUC}\) = change of the AUC, \(\text{AUC}\) = simulated AUC with the original parameter value, \(\Delta p\) = change of the examined model parameter value, \(p\) = original model parameter value.
2 Results

2.1 Idarucizumab model

Predicted versus observed plasma concentration-time profiles and fractions excreted to urine of all available studies are presented in Figs. S2-S4. Corresponding MRD values of predicted plasma concentrations and GMFE values of areas under the plasma concentration-time curves are listed in Tables S5 and S6, respectively. For the description of idarucizumab pharmacokinetics in Japanese individuals, the GFR fraction is reduced from 0.32 to 0.26. Figs. S5 and S6 and corresponding MRD values in Table S4 show that this adaption significantly improved the predictions. Results of the sensitivity analysis are shown in Fig. S7, demonstrating that the only parameter values the model is (equally) sensitive to, are GFR and GFR fraction.

Fig. S2 Predicted versus observed idarucizumab plasma concentrations in healthy Caucasian individuals, following administration of different doses (20 - 8000 mg) as 60 min infusions [11]. Clinically observed data are shown as dots; solid lines illustrate the predicted plasma concentrations. IDA: idarucizumab
Fig. S3 Idarucizumab plasma concentrations (dark blue) and fractions excreted to urine (light blue) following administration of different doses as bolus injection or 60 min infusion to a/b: healthy Caucasian individuals [4,10], c/d: Caucasian individuals between 45 and 64 years of age, pre-treated with 220 mg dabigatran etexilate bid [8,15], e: Caucasian individuals with moderate renal impairment, pre-treated with 150 mg dabigatran etexilate bid [8,15] and f/g: healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; solid lines illustrate the predicted plasma concentrations, dashed lines illustrate the predicted fractions excreted to urine. bid: twice a day, DE: dabigatran etexilate, fe to urine: fraction excreted to urine, IDA: idarucizumab, inf: infusion, RI: renal impairment
Fig. S4 Idarucizumab plasma concentrations in dabigatran patients [17]. 2x 2500 mg idarucizumab were applied as bolus injections to patients a: with life-threatening bleeding, b: requiring emergency surgery, c: with normal renal function, d: with mild renal impairment, e: with moderate renal impairment or f: with severe renal impairment. Clinically observed data are shown as dots; solid lines illustrate the predicted plasma concentrations. DAB: dabigatran, IDA: idarucizumab, RI: renal impairment
Fig. S5 Idarucizumab plasma concentrations (dark blue) and fractions excreted to urine (light blue) following administration of different doses (1000 mg – 8000 mg) to healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; lines illustrate the predictions using a GFR fraction of 0.32 (upper row) or 0.26 (lower row). fe to urine: fraction excreted to urine, GFR fraction: fraction of glomerular filtration rate used for passive elimination by the kidney, IDA: idarucizumab, inf: infusion

Fig. S6 Idarucizumab plasma concentrations (dark blue) and fractions excreted to urine (light blue) following administration of different doses (1000 mg – 5000 mg) to healthy Japanese individuals pre-treated with 220 mg dabigatran etexilate twice a day [9,16]. Clinically observed data are shown as dots; lines illustrate the predictions using a GFR fraction of 0.32 (upper row) or 0.26 (lower row). bid: twice a day, DE: dabigatran etexilate, fe to urine: fraction excreted to urine, GFR fraction: fraction of glomerular filtration rate used for passive elimination by the kidney, IDA: idarucizumab, inf: infusion
### Table S4 Mean relative deviation values of the predicted idarucizumab plasma concentrations for Japanese individuals comparing the use of different GFR fractions

| Study            | IDA dose [mg] | DE dose [mg] | MRD (GFR fraction 0.32) | MRD (GFR fraction 0.26) |
|------------------|---------------|--------------|-------------------------|-------------------------|
| Yasaka 2017 [9]  | 1000          | -            | 1.38                    | 1.11                    |
| Yasaka 2017 [9]  | 1000          | 220          | 1.32                    | 1.43                    |
| Yasaka 2017 [9]  | 2000          | -            | 1.47                    | 1.13                    |
| Yasaka 2017 [9]  | 2000          | 220          | 1.70                    | 1.55                    |
| Yasaka 2017 [9]  | 4000          | -            | 1.39                    | 1.10                    |
| Yasaka 2017 [9]  | 4000          | 220          | 1.18                    | 1.38                    |
| Yasaka 2017 [9]  | 2500 + 2500   | 220          | 1.25                    | 1.33                    |
| Yasaka 2017 [9]  | 8000          | -            | 1.39                    | 1.15                    |

MRD (range): \[1.39 \ (1.25-1.70) \quad 1.27 \ (1.10-1.43)\]

GFR fraction: fraction of glomerular filtration rate used for passive elimination by the kidney, IDA: idarucizumab, MRD: mean relative deviation
Table S5 Mean relative deviation values of the predicted idarucizumab plasma concentrations

| Study          | Individual characteristics | IDA dose [mg] | DE dose [mg] | MRD |
|----------------|----------------------------|---------------|--------------|-----|
| Glund 2015 [11]| Healthy Caucasians         | 20            | -            | 1.10|
| Glund 2015 [11]| Healthy Caucasians         | 60            | -            | 1.10|
| Glund 2015 [11]| Healthy Caucasians         | 200           | -            | 1.10|
| Glund 2015 [11]| Healthy Caucasians         | 600           | -            | 1.19|
| Glund 2015 [10]| Healthy Caucasians         | 1000          | 220          | 1.16|
| Glund 2015 [11]| Healthy Caucasians         | 1000          | -            | 1.14|
| Glund 2016 [8] | Caucasians aged 65-80 y    | 1000          | 220          | 1.48|
| Glund 2016 [8] | Caucasians with mild RI    | 1000          | 150          | 1.38|
| Yasaka 2017 [9]| Healthy Japanese           | 1000          | 220          | 1.43|
| Glund 2015 [11]| Healthy Caucasians         | 1200          | -            | 1.11|
| Glund 2015 [10]| Healthy Caucasians         | 2000          | 220          | 1.20|
| Glund 2015 [11]| Healthy Caucasians         | 2000          | -            | 1.08|
| Glund 2015 [11]| Healthy Caucasians         | 2000          | -            | 1.12|
| Yasaka 2017 [9]| Healthy Japanese           | 2000          | 220          | 1.55|
| Glund 2016 [8] | Caucasians aged 45-64 y    | 2500          | 220          | 1.28|
| Glund 2015 [11]| Healthy Caucasians         | 3000          | -            | 1.09|
| Glund 2015 [10]| Healthy Caucasians         | 4000          | 220          | 1.24|
| Glund 2015 [11]| Healthy Caucasians         | 4000          | -            | 1.14|
| Glund 2015 [11]| Healthy Caucasians         | 4000          | -            | 1.20|
| Yasaka 2017 [9]| Healthy Japanese           | 4000          | 220          | 1.38|
| Glund 2016 [8] | Caucasians aged 45-64 y    | 5000          | 220          | 1.10|
| Glund 2016 [8] | Caucasians aged 65-80 y    | 5000          | 220          | 1.29|
| Glund 2016 [8] | Caucasians with mild RI    | 5000          | 150          | 1.56|
| Glund 2016 [8] | Caucasians with moderate RI| 2500 + 2500   | 150          | 1.44|
| Glund 2019 [17]| DE patients with bleeding  | 2500 + 2500   | yes          | 1.33|
| Glund 2019 [17]| DE patients with surgery   | 2500 + 2500   | yes          | 1.36|
| Glund 2019 [17]| DE patients with mild RI   | 2500 + 2500   | yes          | 1.30|
| Glund 2019 [17]| DE patients with severe RI | 2500 + 2500   | yes          | 1.18|
| Glund 2019 [17]| DE patients with moderate RI| 2500 + 2500   | yes          | 1.12|
| Glund 2019 [17]| DE patients with severe RI | 2500 + 2500   | yes          | 1.16|
| Yasaka 2017 [9]| Healthy Japanese           | 2500 + 2500   | 220          | 1.33|
| Glund 2015 [11]| Healthy Caucasians         | 6000          | -            | 1.13|
| Glund 2015 [10]| Healthy Caucasians         | 5000 + 2500   | 220          | 1.24|
| Glund 2015 [11]| Healthy Caucasians         | 8000          | -            | 1.16|
| Yasaka 2017 [9]| Healthy Japanese           | 8000          | -            | 1.15|

MRD (range): 1.24 (1.08-1.56)
MRD < 2: 38/38 studies

DE: dabigatran etexilate, IDA: idarucizumab, MRD: mean relative deviation, RI: renal impairment
| Study             | Patient characteristics | IDA dose [mg] | DE dose [mg] | AUC<sub>obs</sub> [h·µg/mL] | AUC<sub>pred</sub> [h·µg/mL] | AUC<sub>pred</sub> / AUC<sub>obs</sub> |
|-------------------|-------------------------|--------------|--------------|-------------------------------|-------------------------------|---------------------------------|
| Glund 2015 [11]   | Healthy Caucasians      | 20           | -            | 4.25                          | 3.94                          | 0.93                            |
| Glund 2015 [11]   | Healthy Caucasians      | 60           | -            | 17.35                         | 16.46                         | 0.95                            |
| Glund 2015 [11]   | Healthy Caucasians      | 200          | -            | 58.28                         | 57.44                         | 0.99                            |
| Glund 2015 [11]   | Healthy Caucasians      | 600          | -            | 156.93                        | 162.19                        | 1.03                            |
| Glund 2015 [10]   | Healthy Caucasians      | 1000         | 220          | 274.55                        | 300.53                        | 1.09                            |
| Glund 2015 [11]   | Healthy Caucasians      | 1000         | -            | 344.49                        | 317.19                        | 0.92                            |
| Glund 2016 [8]    | Caucasians aged 65-80 y | 1000         | 220          | 352.36                        | 445.56                        | 1.26                            |
| Glund 2016 [8]    | Caucasians with mild RI| 1000         | 150          | 343.08                        | 464.66                        | 1.35                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 1000         | 220          | 393.80                        | 432.80                        | 1.10                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 1000         | -            | 382.01                        | 378.68                        | 0.99                            |
| Glund 2015 [10]   | Healthy Caucasians      | 2000         | 220          | 697.34                        | 625.20                        | 0.90                            |
| Glund 2015 [11]   | Healthy Caucasians      | 2000         | -            | 632.68                        | 631.04                        | 1.00                            |
| Glund 2015 [11]   | Healthy Caucasians      | 2000         | -            | 592.94                        | 603.20                        | 1.02                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 2000         | 220          | 584.83                        | 875.97                        | 1.50                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 2000         | -            | 829.87                        | 875.15                        | 1.05                            |
| Glund 2016 [8]    | Caucasians aged 45-64 y | 2500         | 220          | 1000.79                       | 1061.08                       | 1.06                            |
| Glund 2015 [11]   | Healthy Caucasians      | 3000         | -            | 975.61                        | 964.26                        | 0.99                            |
| Glund 2015 [10]   | Healthy Caucasians      | 4000         | 220          | 1141.73                       | 1296.92                       | 1.14                            |
| Glund 2015 [11]   | Healthy Caucasians      | 4000         | -            | 1321.95                       | 1248.67                       | 0.94                            |
| Glund 2015 [11]   | Healthy Caucasians      | 4000         | -            | 1117.78                       | 1193.34                       | 1.07                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 4000         | 220          | 1510.16                       | 1616.58                       | 1.07                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 4000         | -            | 1557.38                       | 1739.95                       | 1.12                            |
| Glund 2016 [8]    | Caucasians aged 45-64 y | 5000         | 220          | 1216.27                       | 1691.15                       | 1.39                            |
| Glund 2016 [8]    | Caucasians aged 65-80 y | 5000         | 220          | 1965.53                       | 2373.93                       | 1.21                            |
| Glund 2016 [8]    | Caucasians with mild RI| 5000         | 150          | 1789.79                       | 2459.63                       | 1.37                            |
| Glund 2016 [8]    | Caucasians with moderate RI | 2500 + 2500 | 150      | 2849.93                       | 3241.90                       | 1.14                            |
| Glund 2019 [17]   | DE patients with bleeding| 2500 + 2500 | yes        | 2354.73                       | 3087.36                       | 1.31                            |
| Glund 2019 [17]   | DE patients with surgeries | 2500 + 2500 | yes      | 2133.34                       | 2144.74                       | 1.01                            |
| Glund 2019 [17]   | DE patients with bleeding| 2500 + 2500 | yes        | 2902.07                       | 2316.37                       | 0.80                            |
| Glund 2019 [17]   | DE patients with mild RI | 2500 + 2500 | yes        | 3846.41                       | 2498.09                       | 0.65                            |
| Glund 2019 [17]   | DE patients with moderate RI | 2500 + 2500 | yes     | 4964.84                       | 3624.39                       | 0.73                            |
| Glund 2019 [17]   | DE patients with severe RI | 2500 + 2500 | yes      | 4888.68                       | 4276.85                       | 0.87                            |
| Yasaka 2017 [9]   | Healthy Japanese        | 2500         | 220          | 1742.69                       | 2189.93                       | 1.26                            |
| Study                | Population            | Dose (mg) | Time (h) | Observed | Predicted | GMFE |
|----------------------|-----------------------|-----------|----------|-----------|-----------|------|
| Glund 2015 [11]      | Healthy Caucasians    | 6000      | -        | 1808.52   | 1925.41   | 1.06 |
| Glund 2015 [10]      | Healthy Caucasians    | 5000 + 2500 | 220     | 2906.85   | 2307.85   | 0.79 |
| Glund 2015 [11]      | Healthy Caucasians    | 8000      | -        | 2785.73   | 2574.43   | 0.92 |
| Yasaka 2017 [9]      | Healthy Japanese      | 8000      | -        | 2631.26   | 2635.32   | 1.00 |

**GMFE (range):** 1.14 (1.00 - 1.54)

**GMFE < 2:** 38/38 studies

AUC: area under the plasma concentration-time curve, DE: dabigatran etexilate, GMFE: geometric mean fold error, IDA: idarucizumab, obs: observed, pred: predicted, RI: renal impairment
**Fig. S7** Idarucizumab model sensitivity analysis. Sensitivity of the predicted AUC$_{0-\infty}$ to single model parameters, simulating a 5000 mg idarucizumab bolus injection. A sensitivity value of 1.0 indicates that a 100% change of the examined parameter value causes a 100% change of the predicted AUC$_{0-\infty}$. GFR: glomerular filtration rate, GFR 50: glomerular filtration rate needed to reach half of the maximum kcat, kcat: catalytic rate constant (turnover number), Km: Michaelis-Menten constant, ref conc: reference concentration.
2.2 Idarucizumab-dabigatran interaction model

Before the implementation of the idarucizumab-dabigatran (glucuronide) interaction, the performance of the dabigatran model was evaluated. Figs. S10a and S10b show goodness-of-fit plots of dabigatran plasma concentrations and dabigatran fractions excreted to urine, without the co-administration of idarucizumab. Corresponding MRD values are listed in Table S7. The model MRD of 1.33 (1.14-1.57), with MRDs for all studies well below the 2-fold prediction acceptance limit, demonstrates the good model performance. To account for the interindividual variability of the pharmacokinetics of dabigatran, mainly caused by its highly variable bioavailability, dabigatran etexilate doses were adjusted to match the observed data before idarucizumab co-administration. These dose adjustments were all < 25% of the reported dabigatran etexilate doses. Goodness-of-fit plots of the predictions after this dose adjustment are shown in Figs. S10c and S10d, with the corresponding MRD values also listed in Table S7.

Plots presenting predicted compared to observed plasma concentration-time profiles and fractions excreted to urine of dabigatran and idarucizumab during co-administration, are presented in Figs. S8 and S9. These plots demonstrate that the model adequately predicts the drastic reduction of dabigatran plasma concentrations after the administration of idarucizumab. The corresponding co-administration MRD values are listed in Table S7.
Fig. S8 Plasma concentrations (upper row) and fractions excreted to urine (lower row) of dabigatran (orange) and idarucizumab (blue) during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 74 h, arrow) in elderly Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid and dashed lines illustrate the model predictions. bid: twice a day, DAB: dabigatran, DE: dabigatran etexilate, fe to urine: fraction excreted to urine, IDA: idarucizumab, unb sum: dabigatran and dabigatran glucuronide unbound to plasma proteins and idarucizumab.

Fig. S9 Plasma concentrations (upper row) and fractions excreted to urine (lower row) of dabigatran (orange) and idarucizumab (blue) during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 242 h, arrow) in healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; solid and dashed lines illustrate the model predictions. bid: twice a day, DAB: dabigatran, DE: dabigatran etexilate, fe to urine: fraction excreted to urine, IDA: idarucizumab, unb sum: dabigatran and dabigatran glucuronide unbound to plasma proteins and idarucizumab, unconj: not glucuronidated dabigatran.
Fig. S10 Goodness-of-fit plots of dabigatran plasma concentrations (left column) and fractions excreted to urine (right column), without co-administration of idarucizumab. Shown are the predicted compared to observed data a/b: before and c/d: after adjustment of the dabigatran etexilate doses. The line of identity is shown as solid line; the 0.8 to 1.25-fold bioequivalence limits are shown as dotted lines; the 0.5 to 2.0-fold prediction acceptance limits are shown as dashed lines. DAB: dabigatran, fe to urine: fraction excreted to urine, obs: observed, pred: predicted
Table S7 Mean relative deviation values of the predicted dabigatran plasma concentrations before and after adjustment of the administered dabigatran etexilate doses, without and with co-administration of idarucizumab

| Study           | Individual characteristics | IDA dose [mg] | MRD (no dose adjustment) | MRD (dose adjustment) |
|-----------------|----------------------------|---------------|---------------------------|-----------------------|
| **Without idarucizumab co-administration** |                            |               |                           |                       |
| Glund 2015 [10] | Healthy Caucasians a       | -             | 1.14                      | 1.18                  |
| Glund 2015 [10] | Healthy Caucasians a       | -             | 1.24                      | 1.10                  |
| Glund 2015 [10] | Healthy Caucasians a       | -             | 1.34                      | 1.14                  |
| Glund 2015 [10] | Healthy Caucasians a       | -             | 1.22                      | 1.12                  |
| Glund 2016 [8]  | Caucasians with mild RI b  | -             | 1.31                      | 1.27                  |
| Glund 2016 [8]  | Caucasians with mild RI b  | -             | 1.34                      | 1.19                  |
| Glund 2016 [8]  | Caucasians with moderate RI b | -          | 1.35                      | 1.33                  |
| Glund 2016 [8]  | Caucasians aged 45-64 y a  | -             | 1.51                      | 1.30                  |
| Glund 2016 [8]  | Caucasians aged 45-64 y a  | -             | 1.38                      | 1.26                  |
| Glund 2016 [8]  | Caucasians aged 65-80 y a  | -             | 1.46                      | 1.18                  |
| Glund 2016 [8]  | Caucasians aged 65-80 y a  | -             | 1.35                      | 1.21                  |
| Yasaka 2017 [9] | Healthy Japanese a         | -             | 1.23                      | 1.22                  |
| Yasaka 2017 [9] | Healthy Japanese a         | -             | 1.25                      | 1.16                  |
| Yasaka 2017 [9] | Healthy Japanese a         | -             | 1.28                      | 1.23                  |
| Yasaka 2017 [9] | Healthy Japanese a         | -             | 1.57                      | 1.26                  |

**MRD (range):**

- MRD < 2: 1.33 (1.14-1.57) 15/15 1.21 (1.10-1.33) 15/15

| Study           | Individual characteristics | IDA dose [mg] | MRD (no dose adjustment) | MRD (dose adjustment) |
|-----------------|----------------------------|---------------|---------------------------|-----------------------|
| **With idarucizumab co-administration** |                            |               |                           |                       |
| Glund 2015 [10] | Healthy Caucasians a       | 1000          | 2.18                      | 1.76                  |
| Yasaka 2017 [9] | Healthy Japanese a         | 1000          | 3.87                      | 1.50                  |
| Glund 2016 [8]  | Caucasians aged 65-80 y a  | 1000          | 9.23                      | 2.89                  |
| Glund 2016 [8]  | Caucasians with mild RI b  | 1000          | 2.24                      | 1.70                  |
| Glund 2015 [10] | Healthy Caucasians a       | 2000          | 4.01                      | 3.12                  |
| Yasaka 2017 [9] | Healthy Japanese a         | 2000          | 3.64                      | 1.82                  |
| Glund 2016 [8]  | Caucasians aged 45-64 y a  | 2500          | 3.74                      | 2.39                  |
| Glund 2015 [10] | Healthy Caucasians a       | 4000          | 2.07                      | 1.54                  |
| Yasaka 2017 [9] | Healthy Japanese a         | 4000          | 6.23                      | 1.56                  |
| Yasaka 2017 [9] | Healthy Japanese a         | 2500 + 2500   | 1.63                      | 5.10                  |
| Glund 2016 [8]  | Caucasians aged 45-64 y a  | 5000          | 2.09                      | 1.46                  |
| Glund 2016 [8]  | Caucasians aged 65-80 y a  | 5000          | 1.49                      | 1.64                  |
| Glund 2016 [8]  | Caucasians with mild RI b  | 5000          | 1.88                      | 2.22                  |
| Glund 2016 [8]  | Caucasians with moderate RI b | 2500 + 2500 | 1.94                      | 2.09                  |
| Glund 2015 [10] | Healthy Caucasians a       | 5000 + 2500   | 1.39                      | 1.38                  |

**MRD (range):**

- MRD < 2: 3.17 (1.39-9.23) 5/15 2.14 (1.38-5.10) 10/15

*a dabigatran etexilate administered in doses of 220 mg twice a day
*b dabigatran etexilate administered in doses of 150 mg twice a day
IDA: idarucizumab, MRD: mean relative deviation, RI: renal impairment
2.3 Idarucizumab-dabigatran pharmacodynamic model

Effect-time profiles of the four coagulation measures aPTT, dTT, ECT and TT during dabigatran administration in healthy and elderly Caucasians, renally impaired Caucasians and healthy Japanese are presented in the following figures, while Figs. S11-S14 present effect-time profiles with co-administration of idarucizumab for dabigatran reversal and Figs. S15-S18 present those without idarucizumab co-administration or co-administration of idarucizumab placebo. Corresponding MRD values of predicted effects are listed in Table S8.
Fig. S11 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 7500 mg, at 74 h, arrow) in healthy Caucasian individuals [4,10]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, TT: thrombin time
Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 74 h, arrow) in healthy, elderly Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, TT: thrombin time
Fig. S13 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (150 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 74 h, arrow) in renally impaired Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, mod: moderate, RI: renal impairment, TT: thrombin time
Fig. S14 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (2000 - 5000 mg, at 242 h, arrow) in healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, TT: thrombin time.
Fig. S15 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days) in healthy Caucasian individuals [4,10]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, TT: thrombin time
Fig. S16 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of placebo (1000 - 5000 mg, at 74 h) in elderly Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, PLAC: placebo, TT: thrombin time
Fig. S17 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (150 mg bid, for 3.5 days), followed by administration of different doses of placebo (1000 - 5000 mg, at 74 h) in renally impaired Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, PLAC: placebo, mod: moderate, RI: renal impairment, TT: thrombin time
Fig. S18 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (150 mg bid, for 3.5 days) in healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, TT: thrombin time.
Table S8 Mean relative deviation values of the predicted coagulation times aPTT, dTT, ECT and TT during treatment with dabigatran etexilate twice a day

| Study         | Individual characteristics | IDA dose [mg] | MRD aPTT | MRD dTT | MRD ECT | MRD TT |
|---------------|-----------------------------|---------------|----------|---------|---------|--------|
| Glund2016 [8] | Caucasians aged 45-64 y a   | -             | 1.08     | 1.05    | 1.28    | 1.26   |
| Glund2016 [8] | Caucasians aged 45-64 y a   | -             | 1.34     | 1.08    | 1.17    | 1.35   |
| Glund2016 [8] | Caucasians aged 65-80 y a   | -             | 1.08     | 1.05    | 1.06    | 1.11   |
| Glund2016 [8] | Caucasians aged 65-80 y a   | -             | 1.12     | 1.07    | 1.11    | 1.18   |
| Glund2016 [8] | Caucasians with mild RI b   | -             | 1.27     | 1.13    | 1.10    | 1.19   |
| Glund2016 [8] | Caucasians with mild RI b   | -             | 1.12     | 1.06    | 1.06    | 1.18   |
| Glund2016 [8] | Caucasians with moderate RI b| -          | 1.08     | 1.09    | 1.10    | 1.11   |
| Yasaka2017 [9]| healthy Japanese a           | -             | 1.18     | 1.10    | 1.11    | 1.22   |
| Yasaka2017 [9]| healthy Japanese a           | -             | 1.18     | 1.08    | 1.07    | 1.25   |
| Yasaka2017 [9]| healthy Japanese a           | -             | 1.08     | 1.08    | 1.08    | 1.26   |
| Yasaka2017 [9]| healthy Japanese a           | -             | 1.09     | 1.08    | 1.09    | 1.24   |
| Glund2015 [10]| healthy Caucasians a         | 1000          | 1.14     | 1.15    | 1.17    | 1.28   |
| Yasaka2017 [9]| healthy Japanese a           | 1000          | 1.08     | 1.05    | 1.10    | 1.20   |
| Glund2016 [8] | Caucasians aged 65-80 y a   | 1000          | 1.35     | 1.25    | 1.06    | 1.71   |
| Glund2016 [8] | Caucasians with mild RI b   | 1000          | 1.35     | 1.15    | 1.33    | 1.47   |
| Glund2015 [10]| healthy Caucasians a         | 2000          | 1.23     | 1.04    | 1.07    | 1.47   |
| Yasaka2017 [9]| healthy Japanese a           | 2000          | 1.19     | 1.06    | 1.09    | 1.39   |
| Glund2016 [8] | Caucasians aged 45-64 y a   | 2500          | 1.25     | 1.23    | 1.07    | 1.72   |
| Glund2015 [10]| healthy Caucasians a         | 4000          | 1.09     | 1.15    | 1.08    | 1.13   |
| Yasaka2017 [9]| healthy Japanese a           | 4000          | 1.09     | 1.07    | 1.05    | 1.21   |
| Yasaka2017 [9]| healthy Japanese a           | 2500 + 2500   | 1.15     | 1.09    | 1.14    | 1.49   |
| Glund2016 [8] | Caucasians aged 45-64 y a   | 5000          | 1.30     | 1.04    | 1.09    | 1.25   |
| Glund2016 [8] | Caucasians aged 65-80 y a   | 5000          | 1.25     | 1.20    | 1.41    | 1.27   |
| Glund2016 [8] | Caucasians with mild RI b   | 5000          | 1.22     | 1.18    | 1.29    | 1.08   |
| Glund2016 [8] | Caucasians with moderate RI b| 5000 + 2500  | 1.06     | 1.21    | 1.38    | 1.15   |
| Glund2015 [10]| healthy Caucasians a         | 5000 + 2500   | 1.13     | 1.05    | 1.31    | 1.06   |

MRD: 1.16 (range: 1.06-1.25) 1.11 (1.04-1.25) 1.16 (1.06-1.40) 1.27 (1.06-1.72)
MRD < 2: 26/26 26/26 26/26 26/26

a dabigatran etexilate administered in doses of 220 mg twice a day
b dabigatran etexilate administered in doses of 150 mg twice a day
aPTT: activated partial thromboplastin time, dTT: diluted thrombin time, ECT: ecarin clotting time, IDA: idarucizumab, MRD: mean relative deviation, RI: renal impairment, TT: thrombin time
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