Clinical Pharmacokinetics

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

Supplementary information

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Running heading: PBPK modeling of dabigatran removal by idarucizumab or hemodialysis

Contents

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 [mg]	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).

$$IDA_{sum} \ [\mu mol/L] = [IDA] \ [\mu mol] \cdot + [IDA\text{-}DAB] \ [\mu mol] + [IDA\text{-}DABG] \ [\mu mol] \tag{1}$$

with IDA_{sum} = sum idarucizumab plasma concentration, [IDA] = idarucizumab plasma concentration, [IDA-DAB] = idarucizumab-dabigatran complex plasma concentration and [IDA-DABG] = idarucizumab-dabigatran glucuronide complex plasma concentration.

$$fe_{IDA \ sum} = \frac{IDA \ [\mu mol] + IDA\text{-}DAB \ [\mu mol] + IDA\text{-}DABG \ [\mu mol]}{IDA_{dose} \ [\mu mol]} \tag{2}$$

with $fe_{IDA \ sum}$ = fraction excreted of sum idarucizumab, IDA, IDA-DAB and IDA-DABG = molar amounts of idarucizumab, idarucizumab-dabigatran complex and idarucizumab-dabigatran glucuronide complex, respectively, that were excreted with the urine and IDA_{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).

$$DAB_{unb\ sum}\ [\mu mol/L] = [DAB]\ [\mu mol/L] \cdot f_{u\ DAB} + [DABG]\ [\mu mol/L] \cdot f_{u\ DABG} \qquad (3)$$

with $DAB_{unb\ sum}$ = unbound sum dabigatran plasma concentration, [DAB] = dabigatran plasma concentration and [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).

$$fe_{unconj\ DAB} = \frac{DAB\ [\mu mol] + IDA\text{-}DAB\ [\mu mol]}{DE_{dose}\ [\mu mol]} \qquad (4)$$

with $fe_{unconj\ DAB}$ = fraction excreted of unconjugated dabigatran, DAB and IDA-DAB = molar amounts of dabigatran and idarucizumab-dabigatran complex excreted with the urine and DE_{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):

$$GFR = c_{p,\,kidney} \cdot GFR_{spec} \cdot m_{kidney} \tag{5}$$

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

$$Q = GFR_{spec} \cdot m_{kidney} \cdot 0.4 \tag{6}$$

$$FlowIntoUrine = c_{p,\,kidney} \cdot Q \tag{7}$$

with Q = filtrate flow rate, GFR_{spec} = glomerular filtration rate of the individual normalized to kidney weight, m_{kidney} = kidney weight and $c_{p,\,kidney}$ = 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.

$$V_{kidney,endo} = V_{kidney,cell} \cdot f_{endo} \tag{8}$$

with $V_{kidney,endo}$ = volume of the endosomal subcompartment of the kidney, $V_{kidney,cell}$ = volume of the intracellular subcompartment of the kidney and f_{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:

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

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

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

$$k_{cat} = \frac{k_{cat,\, max} \cdot GFR_{IND}^n}{GFR\ 50^n + GFR_{IND}^n} \tag{10}$$

with k_{cat} = megalin catalytic rate constant, $k_{cat,\, max}$ = maximum megalin catalytic rate constant, GFR_{IND} = glomerular filtration rate of the respective individual, GFR 50 = glomerular filtration rate needed to reach half of megalin $k_{cat,\, max}$ and n = Hill factor. The parameters of the E_{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]:

$$\frac{dN}{dt} = CL_{spec} \cdot C_{endo} \cdot V_{endo} \tag{11}$$

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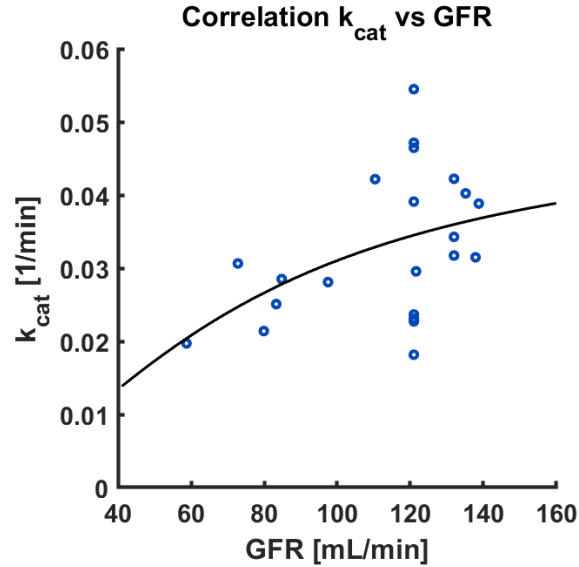
Fig. S1 Megalin k_{cat}, describing the idarucizumab reuptake from the renal tubule lumen into the kidney intracellular endosome, as a function of glomerular filtration rate. Blue circles illustrate the optimized k_{cat} values of each mean individual versus its corresponding reported glomerular filtration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

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

Study	IDA dose [mg]	DE dose [mg]	Reported GFR [mg/mL]	Optimized k_{cat} [1/min]	E_{max} model k_{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_{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):

$$K_{m, IDA}^{app} = K_{m, IDA} \cdot (1 + \frac{[IDA\text{-}DAB]}{K_{i, IDA\text{-}DAB}} + \frac{[IDA\text{-}DABG]}{K_{i, IDA\text{-}DABG}}) \tag{12}$$

with K_m = Michaelis-Menten constant, K_m^{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:

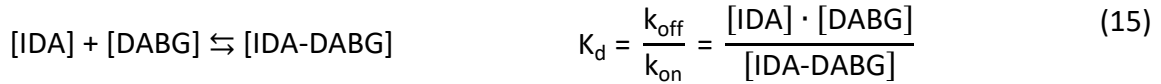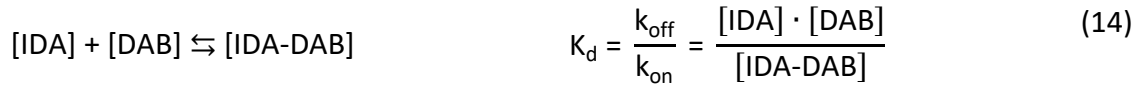$$\frac{dN}{dt} = k_{rec} \cdot C_{endo} \cdot V_{endo} \tag{13}$$

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:

$$[IDA] + [DAB] \leftrightarrows [IDA\text{-}DAB] \qquad K_d = \frac{k_{off}}{k_{on}} = \frac{[IDA] \cdot [DAB]}{[IDA\text{-}DAB]} \qquad (14)$$

$$[IDA] + [DABG] \leftrightarrows [IDA\text{-}DABG] \qquad K_d = \frac{k_{off}}{k_{on}} = \frac{[IDA] \cdot [DABG]}{[IDA\text{-}DABG]} \qquad (15)$$

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_{off} = dissociation rate constant, k_{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]:

$$aPTT = 17.94 \cdot \frac{[DAB]}{0.04 + [DAB]} + 61.67 \cdot [DAB] + 30.21 \qquad (16)$$

$$dTT = 88.30 \cdot [DAB] + 31.59 \qquad (17)$$

$$ECT = 209.70 \cdot [DAB] + 34.85 \qquad (18)$$

$$TT = 106.28 \cdot \frac{[DAB]}{0.19 + [DAB]} + 144.02 \cdot [DAB] + 12.93 \qquad (19)$$

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:

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

with MRD = mean relative deviation, $c_{observed}$ = observed plasma concentration, $c_{predicted}$ = corresponding predicted plasma concentration and n = 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 $AUC_{0-\infty}$ values of the predicted plasma concentration-time profiles were calculated according to:

$$\text{GMFE} = 10^x; \quad x = \left(\sum\left|\log_{10}\left(\frac{AUC_{0-\infty,\ predicted}}{AUC_{0-\infty,\ observed}}\right)\right|\right)/n \tag{21}$$

with GMFE = geometric mean fold error, $AUC_{0-\infty,\ observed}$ = observed area under the plasma concentration-time curve from time point 0 to infinity, $AUC_{0-\infty,\ predicted}$ = corresponding predicted area under the plasma concentration-time curve and n = 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 $AUC_{0-\infty}$ following application of 5000 mg idarucizumab as bolus injection. Parameters were included in the analysis if they have been optimized (K_m, k_{cat}, GFR fraction, solute radius) or if they are associated with optimized parameters (megalin reference concentration, GFR_{50}, $k_{cat,max}$, n, 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):

$$S = \frac{\Delta AUC}{AUC} \cdot \frac{p}{\Delta p} \tag{22}$$

with S = sensitivity of the AUC to the examined model parameter, ΔAUC = change of the AUC, AUC = simulated AUC with the original parameter value, Δp = 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.
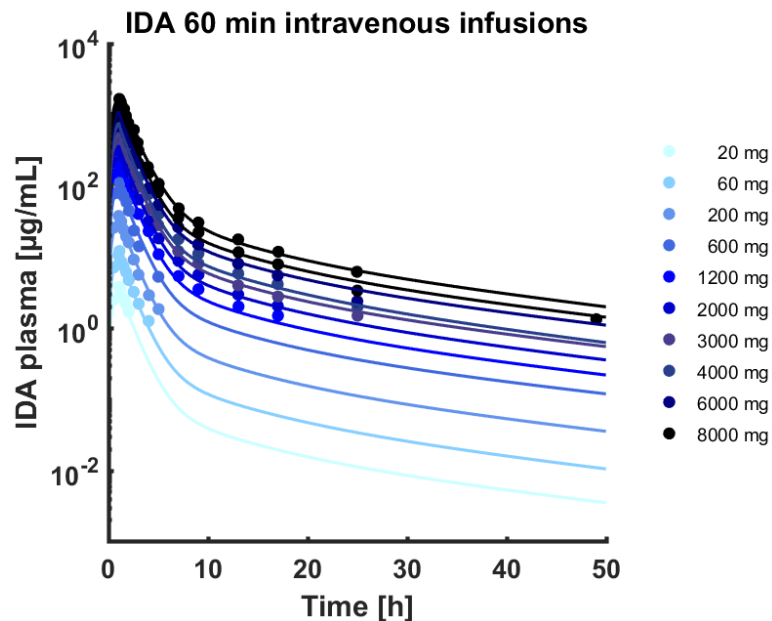
Fig. S2 Predicted versus observed idarucizumab plasma concentrations in healthy Caucasian individuals, following administration of different doses (20 - 8000 mg) as 60 min infusions [11]. Clinically observed data are shown as dots; solid lines illustrate the predicted plasma concentrations. IDA: idarucizumab
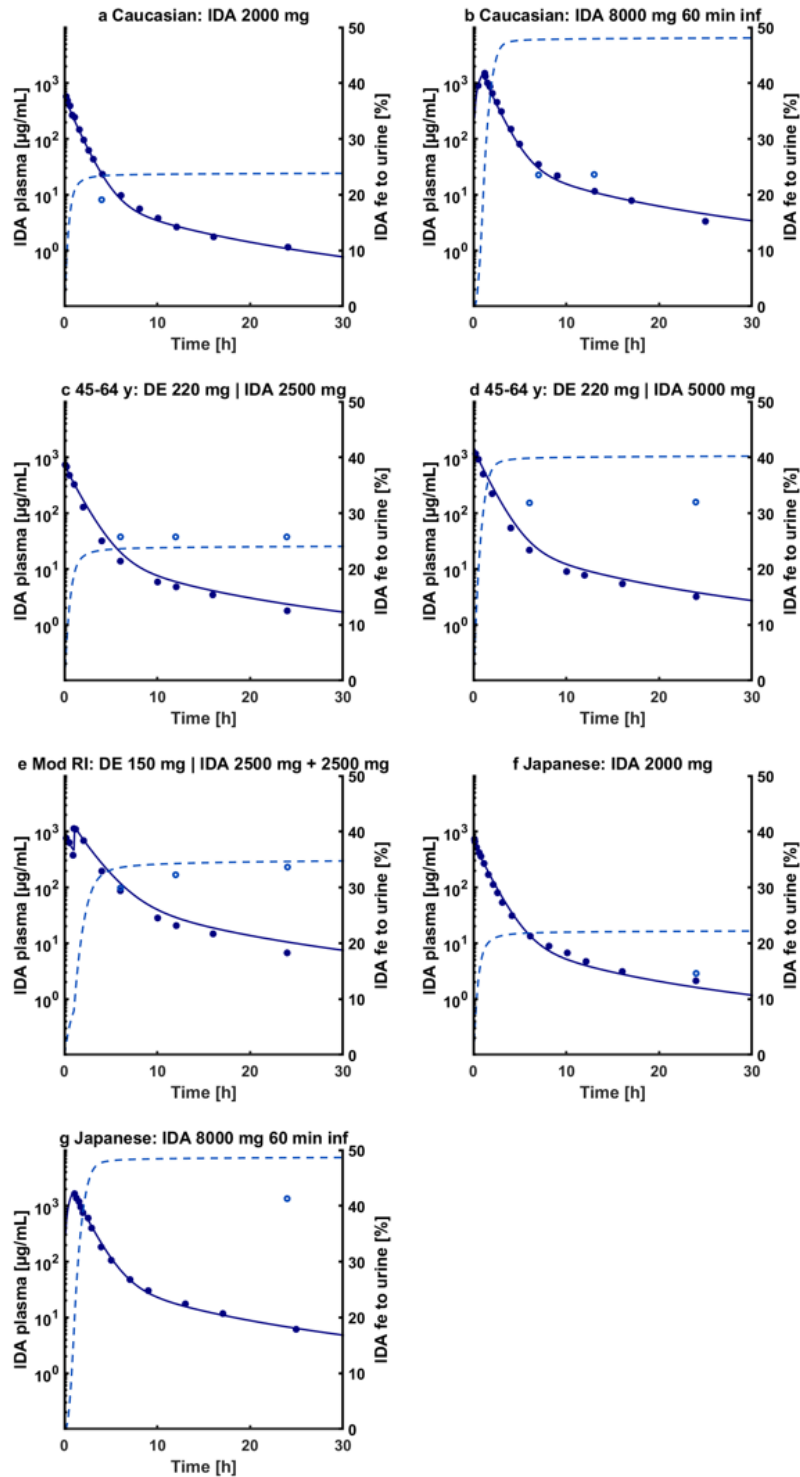
Fig. S3 Idarucizumab plasma concentrations (dark blue) and fractions excreted to urine (light blue) following administration of different doses as bolus injection or 60 min infusion to a/b: healthy Caucasian individuals [4,10], c/d: Caucasian individuals between 45 and 64 years of age, pre-treated with 220 mg dabigatran etexilate bid [8,15], e: Caucasian individuals with moderate renal impairment, pre-treated with 150 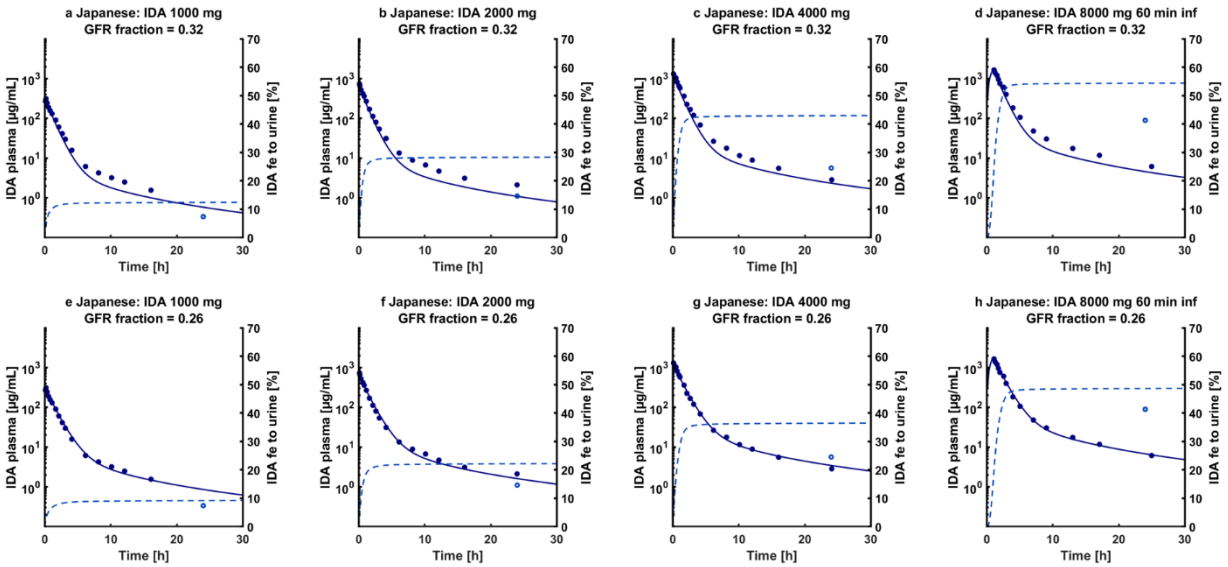mg dabigatran etexilate bid [8,15] and f/g: healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; solid lines illustrate the predicted plasma concentrations, dashed lines illustrate the predicted fractions excreted to urine. bid: twice a day, DE: dabigatran etexilate, fe to urine: fraction excreted to urine, IDA: idarucizumab, inf: infusion, RI: renal impairment
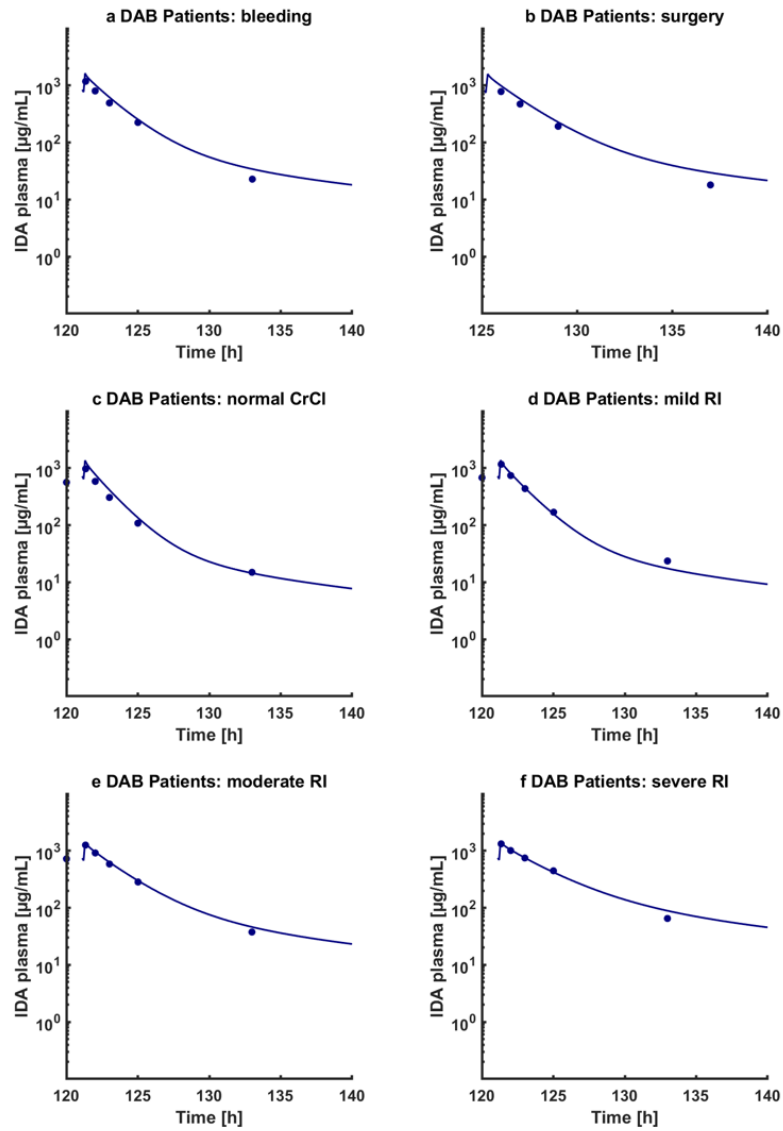
Fig. S4 Idarucizumab plasma concentrations in dabigatran patients [17]. 2x 2500 mg idarucizumab were applied as bolus injections to patients a: with life-threatening bleeding, b: requiring emergency surgery, c: with normal renal function, d: with mild renal impairment, e: with moderate renal impairment 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
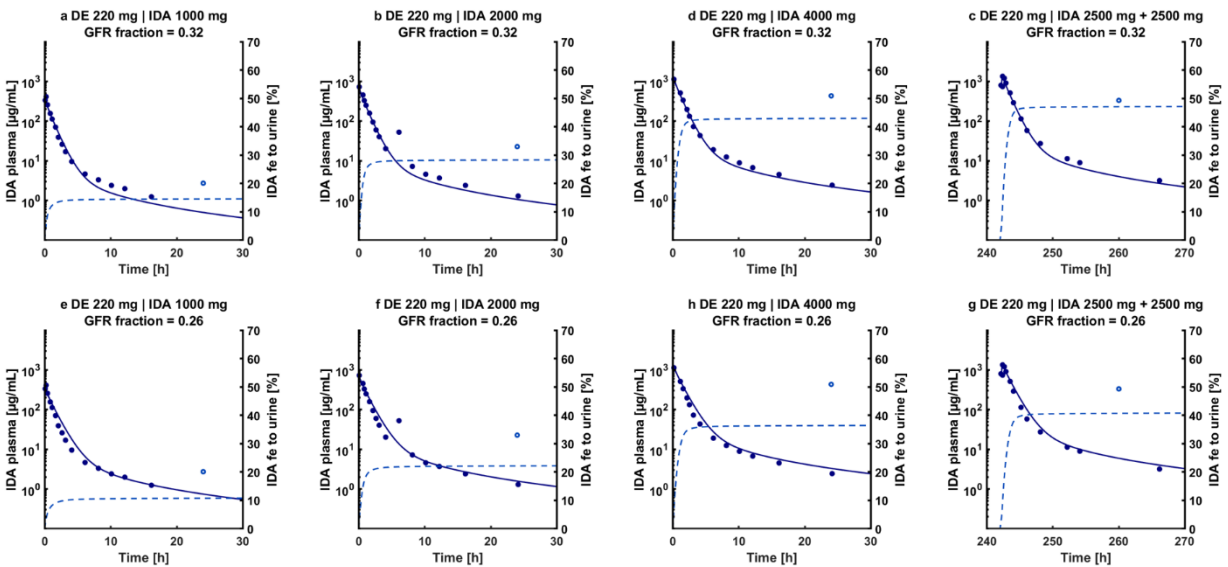
Fig. S5 Idarucizumab plasma concentrations (dark blue) and fractions excreted to urine (light blue) following administration of different doses (1000 mg – 8000 mg) to healthy Japanese individuals [9,16]. Clinically observed data are shown as dots; lines illustrate the predictions using a GFR fraction 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)**	**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
Yasaka 2017 [9]	Healthy Japanese	1000	-	1.11
Glund 2015 [11]	Healthy Caucasians	1200	-	1.13
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
Yasaka 2017 [9]	Healthy Japanese	2000	-	1.16
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
Yasaka 2017 [9]	Healthy Japanese	4000	-	1.10
Glund 2016 [8]	Caucasians aged 45-64 y	5000	220	1.29
Glund 2016 [8]	Caucasians aged 65-80 y	5000	220	1.56
Glund 2016 [8]	Caucasians with mild RI	5000	150	1.46
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 normal renal function	2500 + 2500	yes	1.30
Glund 2019 [17]	DE patients with mild 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

Table S6 Observed and predicted AUC values of idarucizumab with geometric mean fold errors
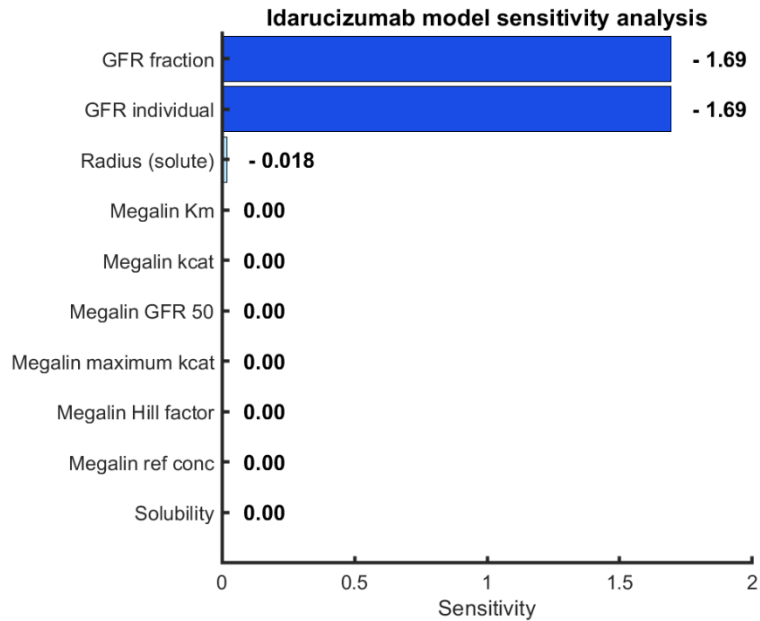
Study	Patient characteristics	IDA dose [mg]	DE dose [mg]	AUC_{obs} [h·µg/mL]	AUC_{pred} [h·µg/mL]	AUC_{pred}/ AUC_{obs}
Glund 2015 [11]	Healthy Caucasians	20	-	4.25	3.94	0.93
Glund 2015 [11]	Healthy Caucasians	60	-	17.35	16.46	0.95
Glund 2015 [11]	Healthy Caucasians	200	-	58.28	57.44	0.99
Glund 2015 [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	-	388.47	426.37	1.10
Glund 2015 [11]	Healthy Caucasians	1200	-	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 normal renal function	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 + 2500	220	1742.69	2189.93	1.26

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

Idarucizumab model sensitivity analysis

Parameter	Sensitivity value
GFR fraction	- 1.69
GFR individual	- 1.69
Radius (solute)	- 0.018
Megalin Km	0.00
Megalin kcat	0.00
Megalin GFR 50	0.00
Megalin maximum kcat	0.00
Megalin Hill factor	0.00
Megalin ref conc	0.00
Solubility	0.00

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), K_m: 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.
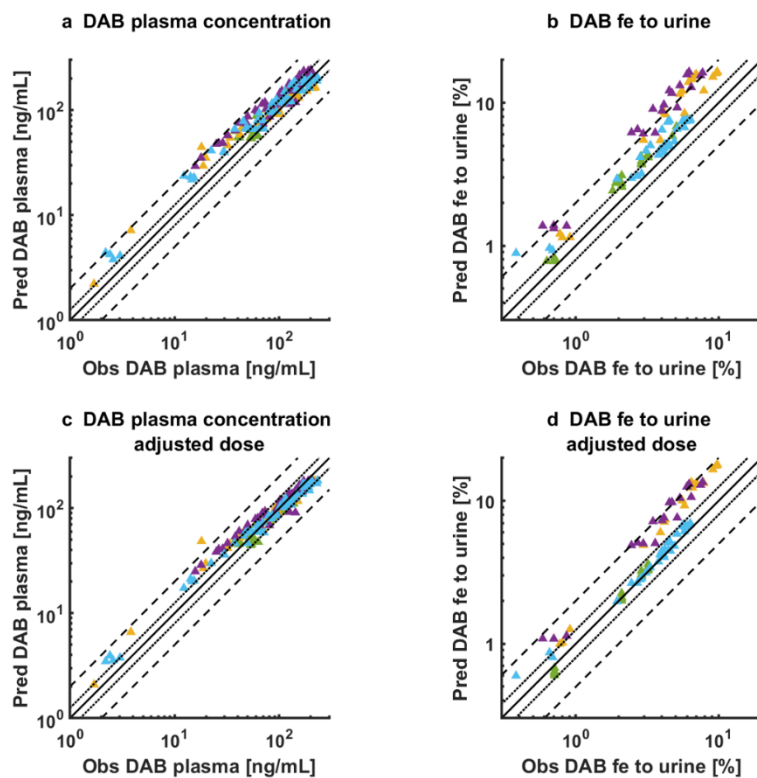
Plots presenting predicted compared to observed plasma concentration-time profiles and fractions excreted to urine of dabigatran and idarucizumab during co-administration, are presented in Figs. S8 and S9. These plots demonstrate that the model adequately predicts the drastic reduction of dabigatran plasma concentrations after the administration of idarucizumab. The corresponding co-administration MRD values are listed in Table S7.
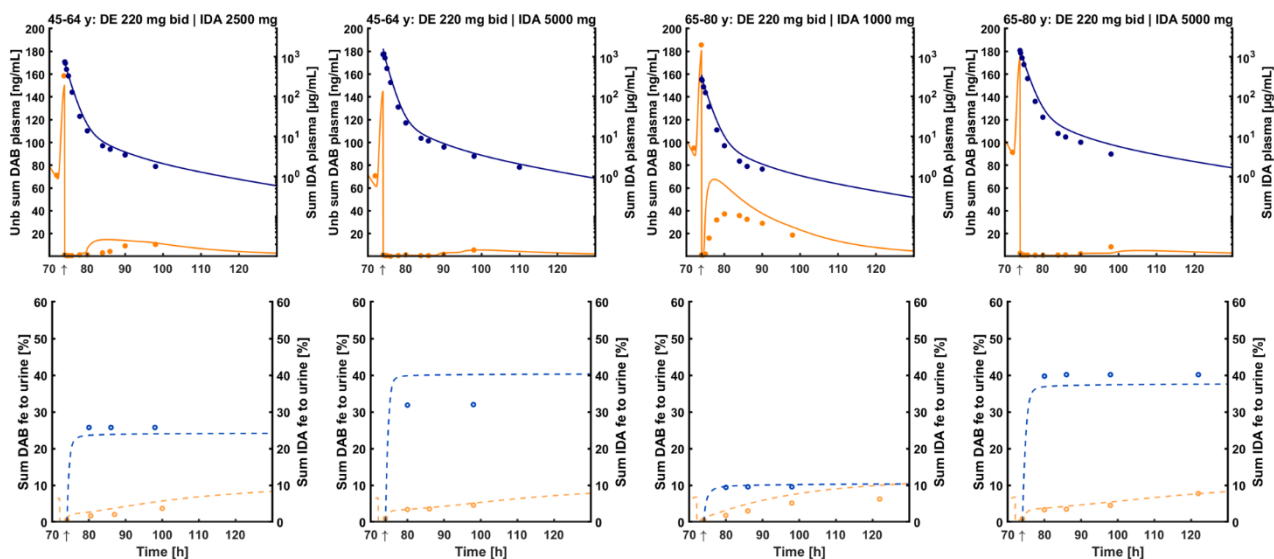
Fig. S8 Plasma concentrations (upper row) and fractions excreted to urine (lower row) of dabigatran (orange) and idarucizumab (blue) during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, 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
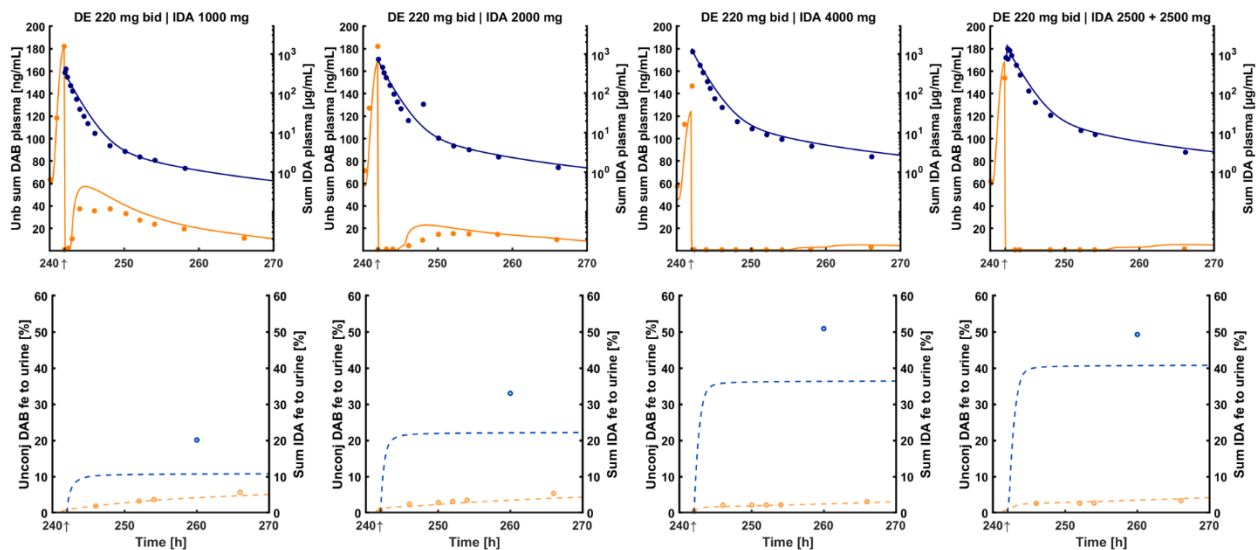
Fig. S9 Plasma concentrations (upper row) and fractions excreted to urine (lower row) of dabigatran (orange) and idarucizumab (blue) during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, 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

23

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):	**1.33 (1.14-1.57)**	**1.21 (1.10-1.33)**
		MRD < 2:	**15/15**	**15/15**
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):	**3.17 (1.39-9.23)**	**2.14 (1.38-5.10)**
		MRD < 2:	**5/15**	**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.
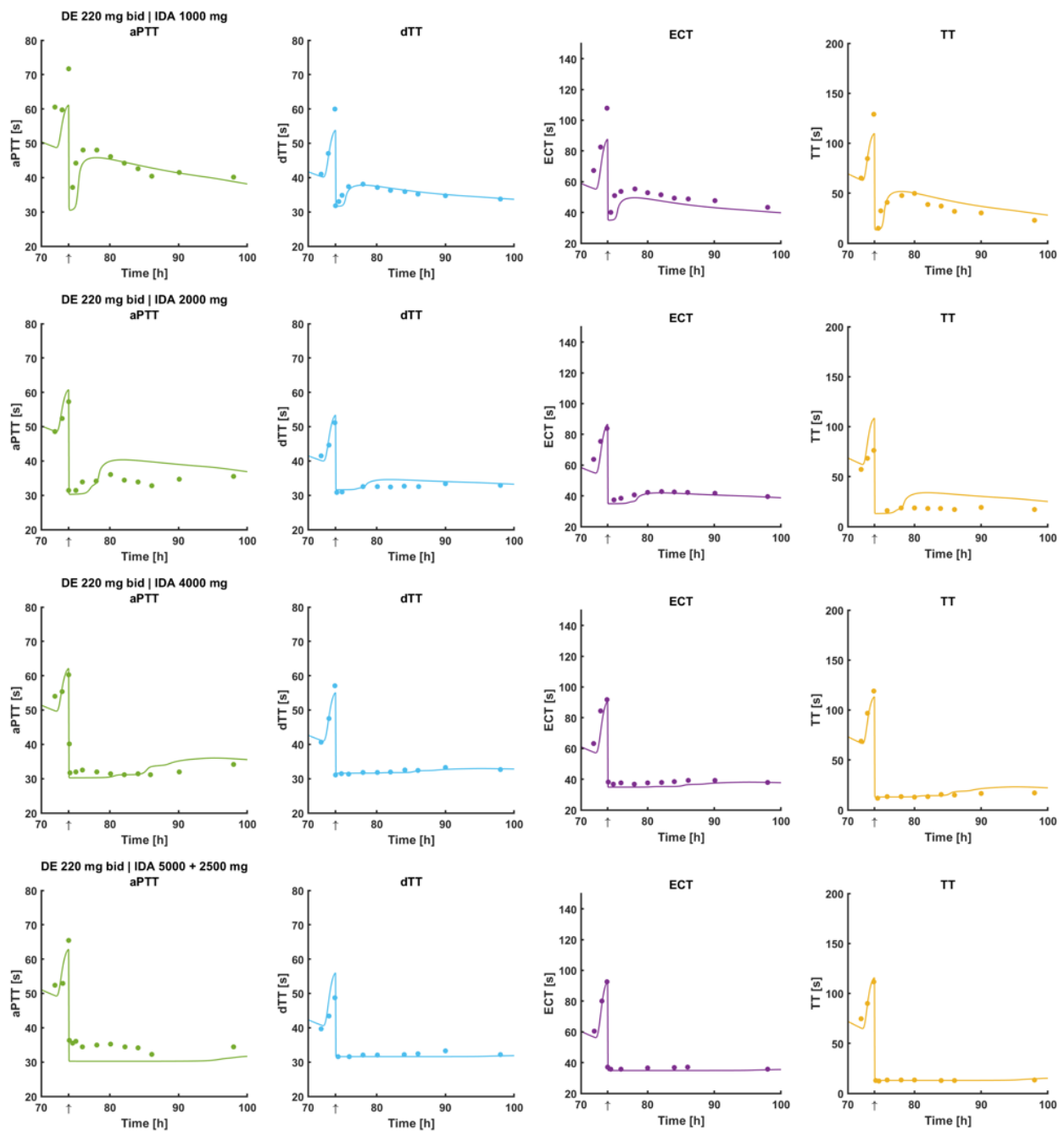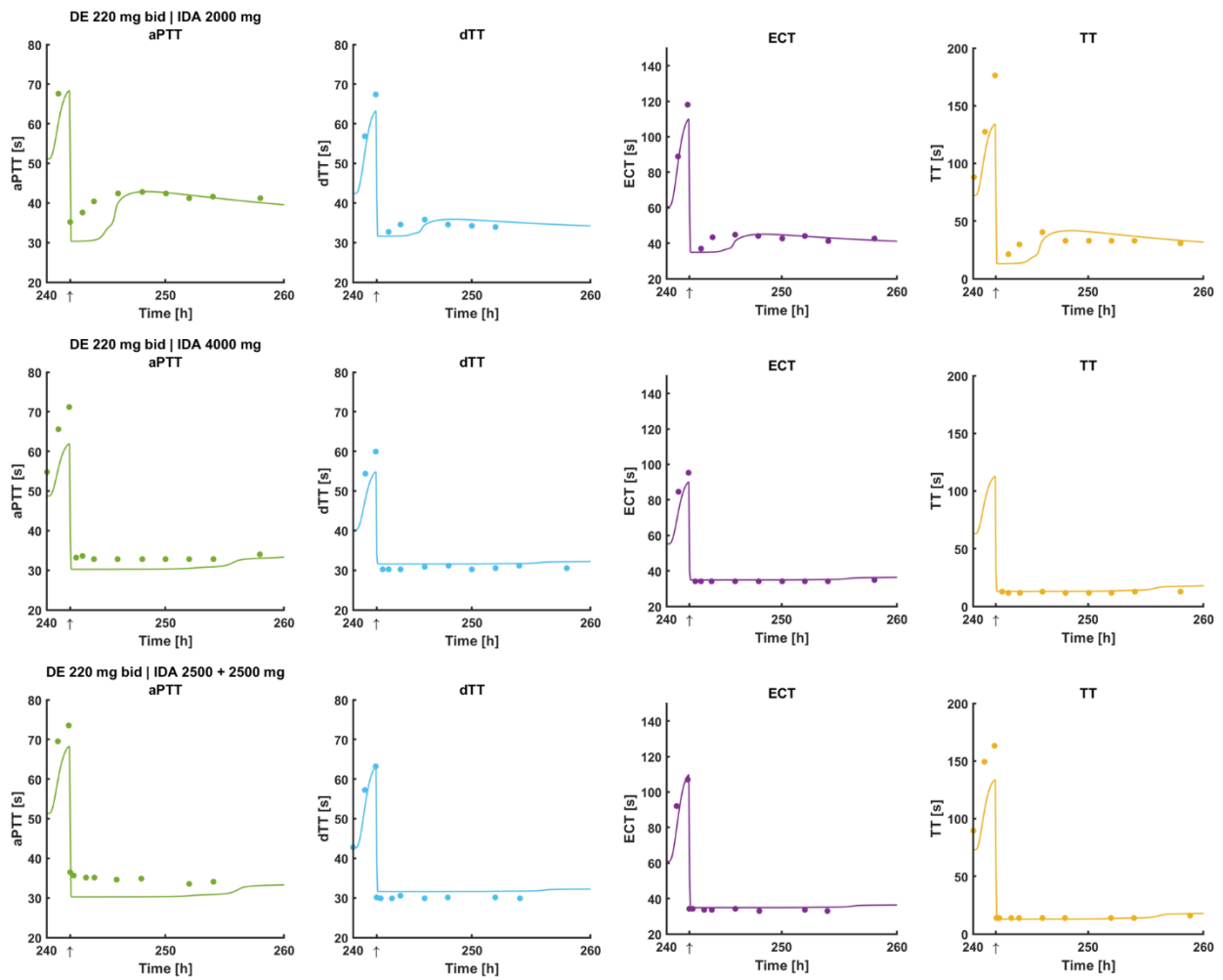
Fig. S11 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 7500 mg, at 74 h, arrow) in healthy Caucasian individuals [4,10]. Clinically observed 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
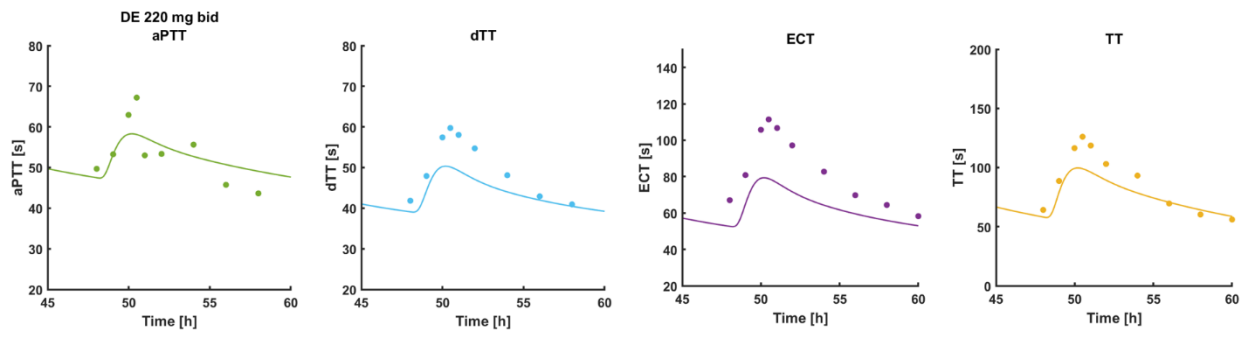
27
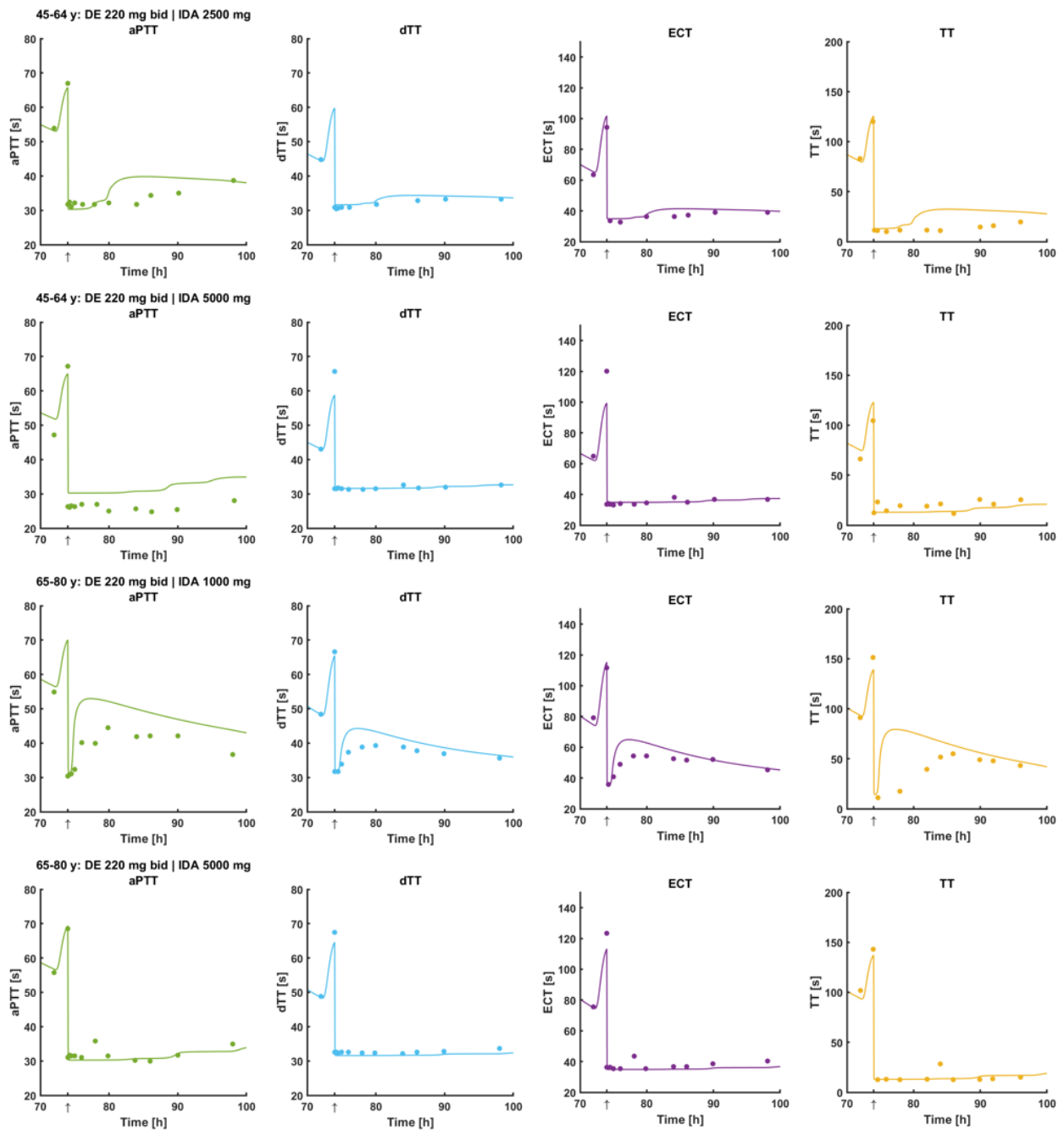
Fig. S12 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 74 h, arrow) in healthy, elderly Caucasian individuals [8,15]. Clinically 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
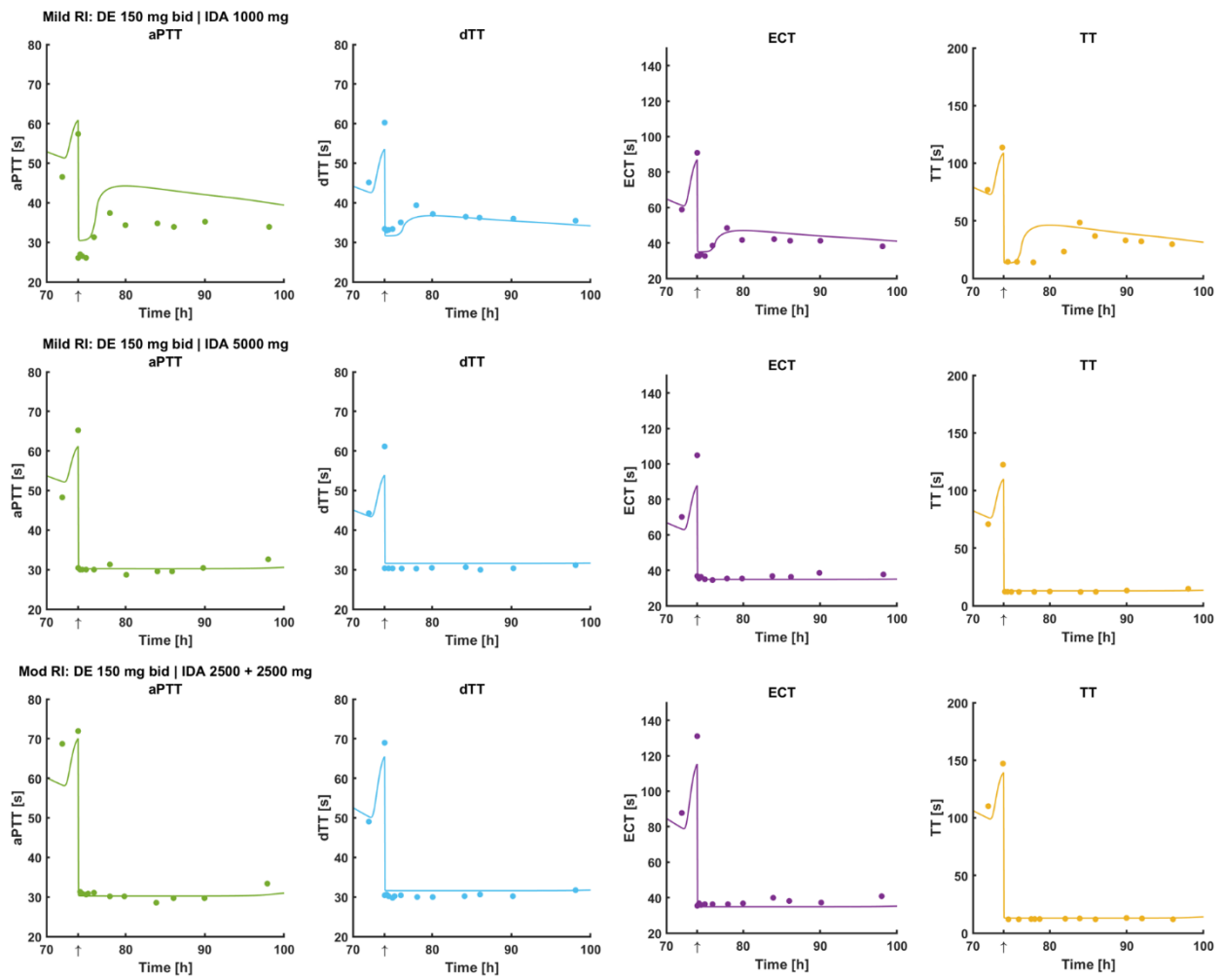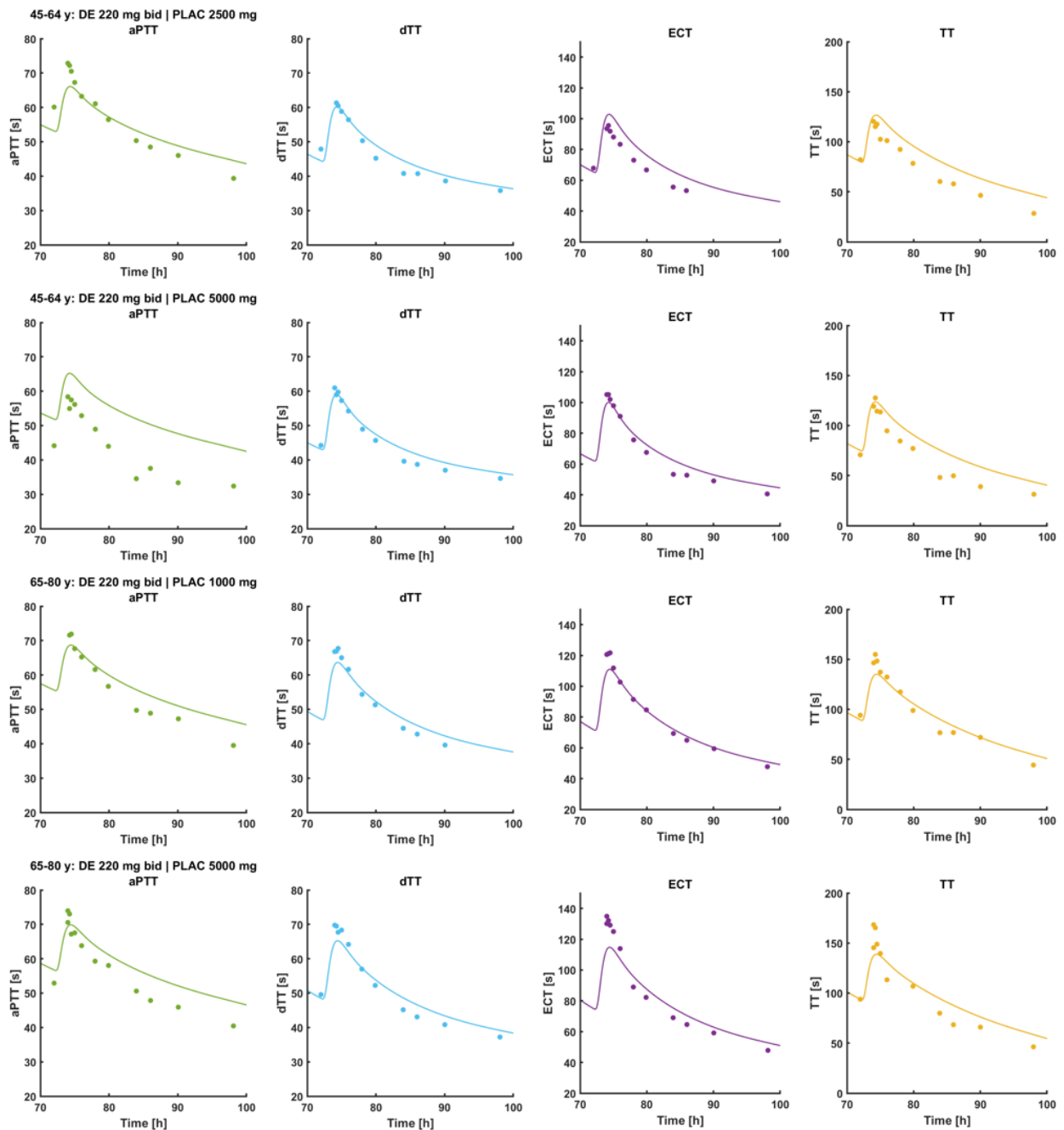
Fig. S13 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (150 mg bid, for 3.5 days), followed by administration of different doses of idarucizumab for dabigatran reversal (1000 - 5000 mg, at 74 h, arrow) in renally impaired Caucasian individuals [8,15]. Clinically 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
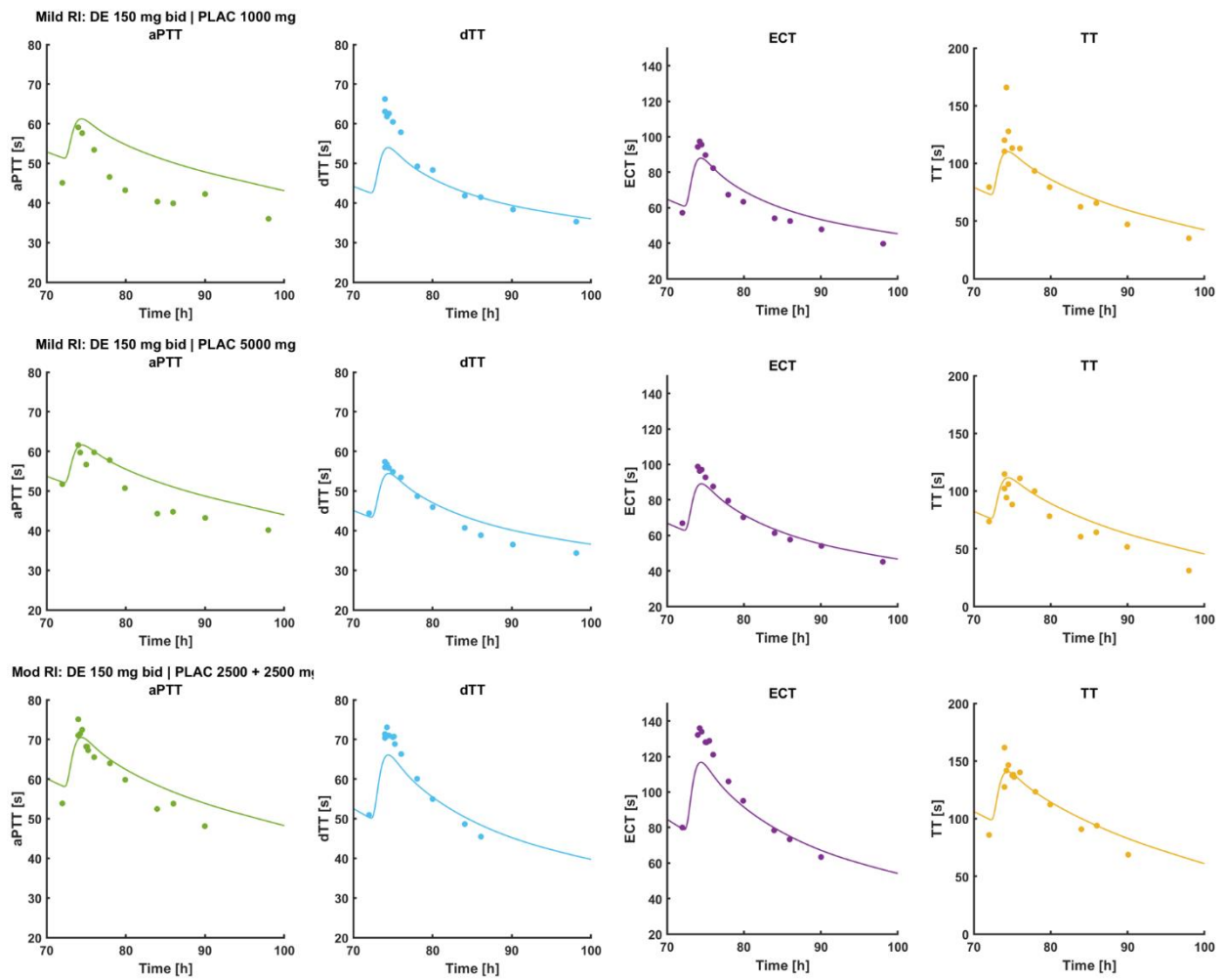
Fig. S15 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days) in healthy Caucasian individuals [4,10]. Clinically observed data are shown as dots; solid lines illustrate the model predictions. aPTT: activated partial thromboplastin time, bid: twice a day, DE: dabigatran etexilate, dTT: diluted thrombin time, ECT: ecarin clotting time, TT: thrombin time
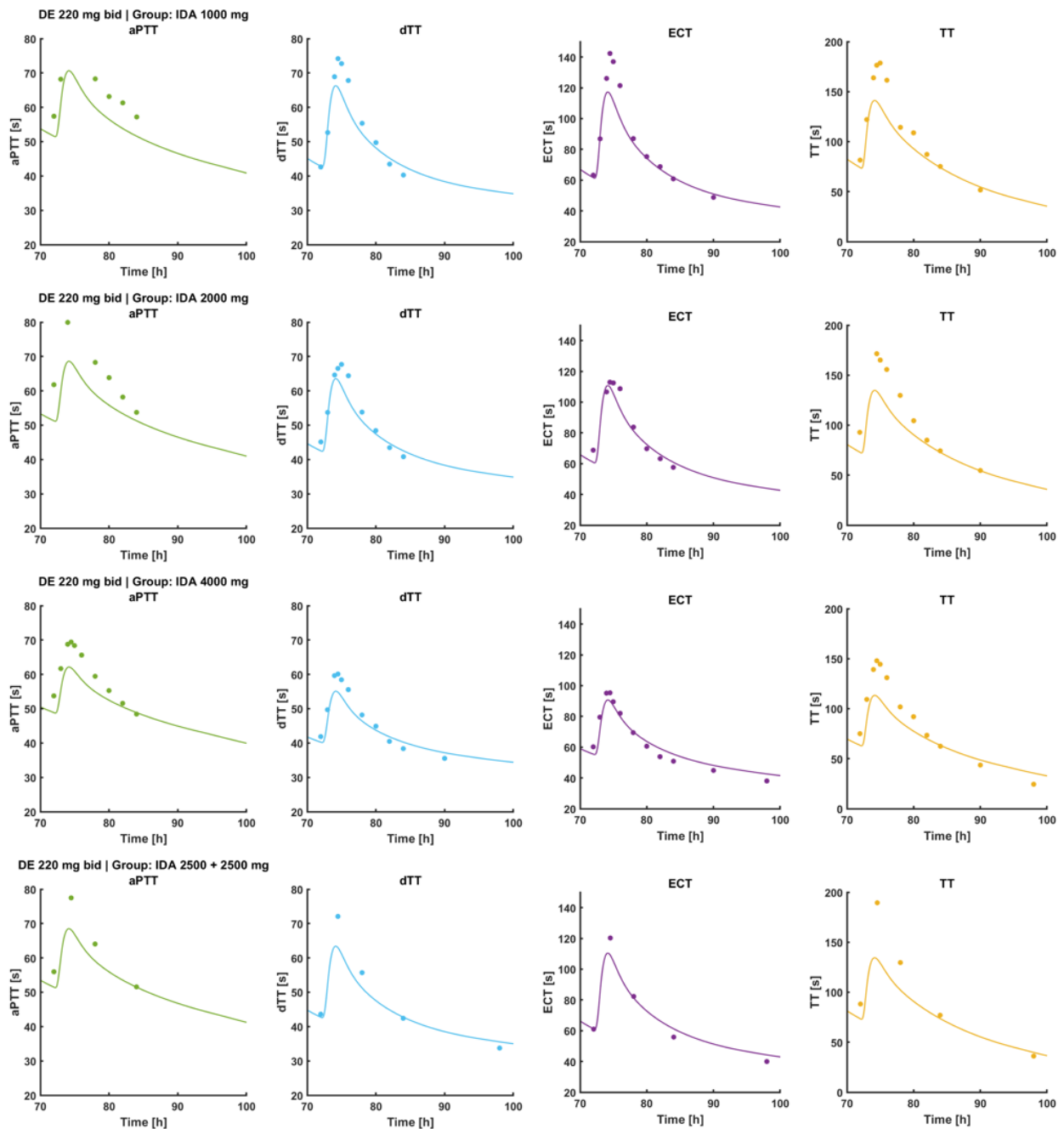
Fig. S16 Effect-time profiles of aPTT, dTT, ECT and TT during dabigatran etexilate treatment (220 mg bid, for 3.5 days), followed by administration of different doses of placebo (1000 - 5000 mg, at 74 h) in elderly Caucasian individuals [8,15]. Clinically observed data are shown as dots; solid lines 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]	2500 + 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**	**1.11**	**1.16**	**1.27**
		(range):	**(1.06-1.35)**	**(1.04-1.25)**	**(1.06-1.40)**	**(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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