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ORIGINAL ARTICLE

Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial

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Summary. *Background:* Dabigatran etexilate (DE) is an orally absorbed prodrug of dabigatran, a thrombin inhibitor that exerts potent anticoagulant and antithrombotic activity. *Objectives:* To characterize the pharmacokinetics of dabigatran in patients with non-valvular atrial fibrillation (AF) from the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial and to quantify the effect of selected factors on pharmacokinetic (PK) model parameters. *Patients and methods:* A total of 27 706 dabigatran plasma concentrations from 9522 patients who received DE 110 or 150 mg twice daily were analyzed with non-linear mixed-effects modeling. *Results:* The pharmacokinetics of dabigatran were best described by a two-compartment disposition model with first-order absorption. The covariates creatinine clearance (CRCL), age, sex, heart failure and the ethnic subgroup 'South Asian' exhibited statistically significant effects on apparent clearance of dabigatran. Body weight and hemoglobin significantly influenced the apparent volume of distribution of the central compartment. Concomitant medication with proton-pump inhibitors, amiodarone and verapamil significantly affected the bioavailability. However, all of the statistically significant factors that were identified, except for renal function status, showed only small to moderate effects (< 26% change in exposure at steady state). On the basis of simulations from the final population PK model, a dose of 75 mg twice daily would result in similar exposure for severely renally impaired patients with CRCL of 15–30 mL min^{-1} and patients with normal renal function receiving 150 mg twice daily. *Conclusions:* The analysis provides a thorough PK characterization of dabigatran in the AF patient population from RE-LY. None of the covariates investigated, with the exception of renal function, warrants dose adjustment.

Keywords: dabigatran etexilate, NONMEM, non-valvular atrial fibrillation, population pharmacokinetics, RE-LY, thrombin inhibitor.

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Introduction

Vitamin K antagonists (VKAs) constitute the primary treatment for the prevention of thromboembolic events in patients with atrial fibrillation (AF), such as stroke. These drugs are difficult to use, owing to slow onset and cessation of action, high interindividual and intraindividual variability in effective plasma concentrations [1], and a high potential for food and drug interactions [2]. As a consequence, the anticoagulant effect in treated patients must be regularly monitored, and dose adjustments may be necessary.

Dabigatran is a novel synthetic, non-peptidic, potent, specific, competitive and reversible inhibitor of thrombin that overcomes the major drawbacks of VKAs. On the basis of the results of the Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial [3], dabigatran can be given as a fixed dose without monitoring. Two blinded doses, 110 and 150 mg twice daily, of dabigatran etexilate (DE) were compared with warfarin locally adjusted to an International Normalized Ratio (INR) of 2.0–3.0, in patients with non-valvular AF. The DE 150-mg dose was superior to dose-adjusted warfarin for the primary outcome of stroke or systemic embolism, and there were similar rates of major hemorrhage between the two groups. The DE 110-mg dose was

non-inferior to warfarin, with lower rates of major hemorrhage in the dabigatran group [3].

Dabigatran is not absorbed orally, but DE, a small molecule prodrug of dabigatran that does not exhibit anticoagulant activity, is orally bioavailable. DE is rapidly absorbed and converted to dabigatran by esterase-catalyzed hydrolysis [4]. Maximum plasma concentrations of dabigatran occur approximately 2–3 h after oral dosing. The disposition is biexponential, the terminal half-life is 12–17 h [5,6], and steady state is attained after 3 days of twice-daily treatment. The total and peak systemic exposure are dose-proportional in the range 50–400 mg twice daily [6]. The oral bioavailability of DE in capsules is 6.5% [6], and shows moderate to high intersubject variability of 31.4% and 53.5% for the area under the plasma concentration–time curve at steady state (AUC_{ss}) in healthy volunteers. Dabigatran is eliminated mainly unchanged (80–85% of the dose) and partially as the glucuronide (20%) via renal glomerular filtration [4,7]. The prodrug DE, but not the active moiety dabigatran, is a substrate of P-glycoprotein (P-GP) [8].

The objective of this analysis was to characterize the population pharmacokinetics (popPK) of dabigatran in AF patients from the RE-LY Phase III trial. In addition, the impacts of selected intrinsic and extrinsic factors on the pharmacokinetics of dabigatran in AF patients were evaluated.

Methods

Study design

The RE-LY study was a prospective randomized open trial with blinded outcome evaluation study with two doses of DE (110 mg twice daily and 150 mg twice daily) as compared with warfarin, adjusted to an INR of 2.0–3.0 [3]. Approximately 6000 patients per treatment group were recruited and randomized. Patients were treated for 2 years, with a further year of follow-up after randomization of the last patient. The primary objective of the trial was to demonstrate the non-inferiority of DE in patients with non-valvular AF for the prevention of stroke and systemic embolism. Patients with severe renal impairment (creatinine clearance [CRCL] < 30 mL min^{-1}) were excluded from this trial. The study was approved by all appropriate national regulatory authorities and ethics committees of the participating centers. Written informed consent was provided by all trial participants before randomization.

For pharmacokinetic (PK) analysis, two blood samples were scheduled for all consenting dabigatran patients at 4 weeks after the start of treatment. Samples were taken before and 2 h $\pm$ 30 min after the morning dose. In a subset of patients (2500 planned), an additional two PK samples were collected after 3, 6 and 12 months of treatment.

Plasma concentrations of total dabigatran after alkaline cleavage of conjugates were determined with a validated HPLC tandem mass spectrometry (HPLC MS/MS) method and used for popPK analysis. The method was validated according to the current Food and Drug Administration guidance on bioanalytical method validation [7,9].

Data analysis

Data analysis was performed with non-linear mixed-effects modeling techniques implemented in the NONMEM software package (version VI, Level 2.0; ICON Development Solutions, Ellicott City, MD, USA). Throughout the analyses, first-order conditional estimation with or without INTERACTION was used. Graphical visualization of NONMEM results and simulations were performed with SAS (version 9.2; SAS Institute, Cary, NC, USA) software.

Model selection was based on several criteria, such as goodness-of-fit plots, precision of model parameter estimates, and the changes in the NONMEM objective function – 2 log likelihood. The model building process was performed stepwise as follows.

Model development The base model of a recent population PK analysis (C. Dansirikul, T. Lehr, K.-H. Liesenfeld, A. Staab, S. Haertter, submitted) was applied to the data, and refined by testing and revising structural and statistical components. CRCL was integrated a priori into the base model. Models were parameterized in terms of apparent clearances (CL/F), apparent volumes of distribution, and absorption parameter(s). Absolute bioavailability (F) was included and fixed to 1, in order to enable the description of interindividual variability in F.

The intrinsic factors (demographics, laboratory values, and health status) and extrinsic factors (comedication) analyzed in this study (Table 1) were prespecified on the basis of physiologic plausibility, statistical significance in the former analyses, and whether they were of general interest. P-GP inhibitors were separated into the single-drug classes of verapamil, amiodarone, or diltiazem. Other P-GP inhibitors and the combination of amiodarone plus verapamil were investigated as additional classes. All preselected covariates were simultaneously added into the base model (full model estimation) [10]. The full covariate model was then subjected to a backward elimination procedure that retained only those covariates for which $P < 0.001$ (1 degree of freedom, χ^2). For categorical covariates with more than two subgroups, combining the groups (e.g. heart failure [HF]) was allowed. Linear and non-linear relationships were investigated for continuous covariates. The most appropriate relationship was selected on the basis of the model selection criteria defined above.

Model evaluation The final model was evaluated by bootstrap analysis and quantitative predictive checks (QPCs). Bootstrap analysis [11] was performed with PERL-SPEAKS-NONMEM (version 2.3.2) [12]. The 500 bootstrap samples were analyzed non-parametrically. For QPCs, 1000 datasets were simulated by use of the final model and its parameters (fixed and random effects). For each dataset, the same number of patients, dosing history, number of observations, sampling scheme and covariate values as in the original data were used. The median trough concentration ($C_{pre,ss}$, defined as 10–16 h after the previous dose) was extracted from both the observed

Table 1 Covariates assessed in the population pharmacokinetic analysis

	Covariate tested on			Rationale for covariate testing		
Covariate investigated	CL/F	F	V_2/F	Physiologically plausible	Statistically significant in former analysis	General interest
Age (years)	X	–	–	X	X	
Weight (kg)	–	–	X	X	X	
Sex	X	–	–	X	X	
Ethnic origin	X	–	–			X*
Creatinine clearance (mL min^{-1})	X	–	–	X	X	
Left ventricular dysfunction	X	–	–		X	
Hemoglobin (g dL^{-1})	–	–	X		X	
Heart failure	X	–	–		X	
New York Heart Association Classification	X	–	–		X†	
P-GP inhibitors	–	X	–	X	X	
Proton-pump inhibitors	–	X	–	X	X	
H_2 receptor antagonists	–	X	–	X		
Verapamil	–	X	–	X		
Amiodarone	–	X	–	X		
Clopidogrel	–	X	–			X‡
Diltiazem	–	X	–			X‡

P-GP, P-glycoprotein. *Only limited data in former analysis. †Classification for heart failure. ‡No data from former analysis.

and each simulated dataset. The distribution of the median of simulated values was constructed, providing the 90% prediction of the median and the deviation of the observed from the simulated median of the 1000 medians.

Simulation The covariate effects were depicted by overlaying the simulated typical profiles for certain covariate values with the 80% prediction interval for the typical RE-LY patient. If one covariate effect was simulated, e.g. comedication taken or CRCL of 30 mL min^{-1}, all other covariates were assumed to be at the median value or not present, e.g. in the case of further comedications. Further simulation scenarios investigated the effect of CRCL on $C_{pre,ss}$ and alternative dosing regimens for patients with severe renal impairment. In addition, the effect of a delayed drug intake on the plasma concentration–time profile of dabigatran was simulated in order to determine a time window that does not result in excessively high peak levels of the following dose.

Results

Dataset description

The PK analysis dataset of the RE-LY study consisted of 9522 patients (65% males) contributing 27 706 plasma concentrations in total. The characteristics of the patient population are shown in Tables 2 and 3. The median age, body weight, hemoglobin level and CRCL of the patients were 72 years, 80.3 kg, 14.3 g dL^{-1}, and 68.4 mL min^{-1}, respectively. The investigated concomitant therapy classes and the percentages of plasma concentrations associated with each class were: P-GP inhibitors, 22.8%; proton-pump inhibitors (PPIs), 13.9%; H_2 receptor antagonists, 4.7%; verapamil, 5.1%; amiodarone, 10.4%; clopidogrel, 2.9%; and diltiazem, 8.4%.

Table 2 Summary of continuous demographic characteristics

Covariate	Mean (SD)	Median	Range
Age (years)	71.2 (8.7)	72	22–97
Body weight (kg)	82.7 (19.5)	80.3	32.7–222.3
Creatinine clearance (mL min^{-1})*	73.2 (27.5)	68.6	16.1–361.4
Hemoglobin (g dL^{-1})	14.2 (1.5)	14.3	4.4–23.3

SD, Standard deviation. *Computed using the Cockroft-Gault equation [17].

PK model

Plasma concentrations of total dabigatran in AF patients were best described by a two-compartment disposition model with first-order absorption and a lag time. Because sampling at only two prespecified time points did not allow description of the complete concentration–time profile, the absorption rate, absorption lag time, intercompartmental clearance and peripheral volume of distribution were fixed to literature values (C. Dansirikul, T. Lehr, K.-H. Liesenfeld, A. Staab, S. Haertter, submitted). A sensitivity analysis justified this procedure. To describe the non-linear relationship between CRCL and CL/F, a hockey stick model (C. Dansirikul, T. Lehr, K.-H. Liesenfeld, A. Staab, S. Haertter, submitted) was first investigated, followed by a power model and an E_{max} model. An E_{max} model with a Hill coefficient best described the data. Covariate analysis was performed for the covariates listed in Table 1 and additional P-GP subgroups as described in Methods. Of 30 covariates/classes included in the full model, nine covariate effects remained significant after backward elimination.

In the final model, age, sex, HF with classes II–IV and South Asian ethnicity were covariates in addition to CRCL that influenced CL/F. Body weight and hemoglobin level were covariates that influenced the apparent volume of distribution in the central compartment (V_2/F). Covariates explaining parts

Table 3 Summary of categorical demographic characteristics (total $N = 9522$)

Covariate	*N*	Percentage
Sex		
Male	6190	65.01
Female	3332	34.99
Ethnicity		
South Asian	283	2.97
Chinese	537	5.64
Japanese	221	2.32
Malay	54	0.57
Other Asian	454	4.77
Arab	29	0.30
Black African	51	0.54
Colored African	19	0.20
European	6616	69.48
Native Latin	498	5.23
Other	760	7.98
LVD		
If not assessed or unknown	4794	50.35
Diagnosis if assessment was performed		
No LVD	2928	30.75
Mild LVD	821	8.62
Moderate LVD	658	6.91
Severe LVD	321	3.37
HF		
If HF was not diagnosed	6483	68.08
If HF was diagnosed	3039	31.92
New York Heart Association classification		
If not diagnosed or unknown	6484	68.09
Class I: patients with no limitation of physical activity. Ordinary activity does not cause undue fatigue, palpitation, dyspnea or angina pain	468	4.91
Class II: patients with slight to moderate limitation of physical activity. They are comfortable at rest	1919	20.15
Class III: patients with marked limitation of physical activity. They are comfortable at rest	596	6.26
Class IV: patients with inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest	55	0.58
Renal status		
Severe impairment (CRCL $<$ 30 mL min^{-1})	33	0.35
Moderate impairment (30 $\leq$ CRCL $<$ 50 mL min^{-1})	1780	18.69
Mild impairment (50 $\leq$ CRCL $<$ 80 mL min^{-1})	4577	48.07
No impairment (80 $\leq$ CRCL $<$ 120 mL min^{-1})	2602	27.33
No impairment (CRCL $>$ 120 mL min^{-1})	530	5.57

CRCL, creatinine clearance; HF, heart failure; LVD, left ventricular dysfunction.

of the variability in F were concomitant medication of verapamil, amiodarone, or PPIs. Table 4 lists the covariate effects and their effects on AUC_{ss}. For a male patient with median values of the continuous covariates and categorical covariates not present (e.g. no cotreatment), the typical CL/F was 69.6 L h^{-1} and the typical V_2/F was 673 L.

The final model parameters are shown in Table 5. All parameters were estimated with good precision (relative standard error [RSE] $\leq$ 13.2%) The goodness-of-fit plots are shown in Fig. 1. The epsilon-shrinkage was 15.0%.

Model evaluation and simulation

The population parameter estimates were similar to the median of the 500 bootstrap replicates with a relative bias between − 0.25% and + 1.23%, and were within the 95% confidence intervals obtained from the bootstrap analysis. These results suggested unbiased parameter estimates of the developed model.

A QPC showed that the dose normalized trough concentrations at steady state were slightly underpredicted, with a deviation of 5.6%. However, because of the large amount of data, the 90% prediction intervals for the median $C_{pre,ss}$ are very narrow, and the observed median was slightly outside the 90% prediction interval. In addition, QPC results stratified by covariates also showed good predictive performance in the subgroups (Table S1). All subgroups except one deviated by less than ± 10%. Typical plasma concentration–time profiles for patients with covariates at the far end of the distribution (1st or 99th percentile) were simulated (Fig. 2). Except for patients on the borderline for severe renal impairment (CRCL near 30 mL min^{-1}), all investigated effects were clearly within the 80% prediction interval for a typical AF patient.

In order to illustrate the magnitude of the strongest covariate effect on dabigatran plasma concentrations, the relationship between CRCL and trough levels ($C_{pre,ss}$) was simulated for

Table 4 Effect of covariates on model parameters and on area under the plasma concentration–time curve at steady state (AUC_{ss})

Covariate	Effect on model parameters	Effect on AUC_{ss}
CRCL	Increase in CL/F according to an E_{max} function with E_{max} = 124 L h^{-1}, EC_{50} = 56.7 mL min^{-1} and power = 1.29. CL/F increases with increasing CRCL	Patients with CRCL of 30 and 50 mL min^{-1} have a 1.8-fold and 1.2-fold increased AUC_{ss}, respectively, as compared with the median CRCL of 69 mL min^{-1}
Age	Decrease of 0.41% in CL/F per year older than the median of 72 years (and vice versa)	A 97-year-old patient has an approximately 11.5% increased AUC_{ss} as compared with a 72-year-old patient
Sex	Decrease of 8.3% in CL/F in female patients	Females have a 9.1% increased AUC_{ss} as compared with male patients
South Asian	Decrease of 20.3% in CL/F in the ethnic group of South Asian patients	AUC_{ss} is increased by 25.5% in South Asians as compared with other ethnicities
HF	Decrease of 6.7% in CL/F in patients with HF of class II, III, or IV	AUC_{ss} is increased by 7.2% in patients with HF of class II–IV as compared with patients without HF or with class I HF
Weight	Increase of 0.77% in V_2/F per 1-kg increase above the median weight of 80 kg (and vice versa)	Weight has no effect on AUC_{ss}
Hemoglobin	Decrease of 4.0% in V_2/F per 1 g dL^{-1} increase above the median hemoglobin concentration of 14.3 g dL^{-1} (and vice versa)	Hemoglobin has no impact on AUC_{ss}
Verapamil	Increase of 23% in bioavailability with coadministration of verapamil	Patients with coadministration of verapamil have 23% increased AUC_{ss}
Amiodarone	Increase of 12% in bioavailability with coadministration of amiodarone	Patients with coadministration of amiodarone have 12% increased AUC_{ss}
PPIs	Decrease of 12.5% in bioavailability with coadministration of PPI	Patients with coadministration of PPI have 12.5% decreased AUC_{ss}

CRCL, creatinine clearance; HF, heart failure; PPI, proton-pump inhibitor. For the calculation of the effect of a particular covariate, all other covariates are assumed to have no effect (i.e. either at the median value or not present, e.g. in case of comedications).

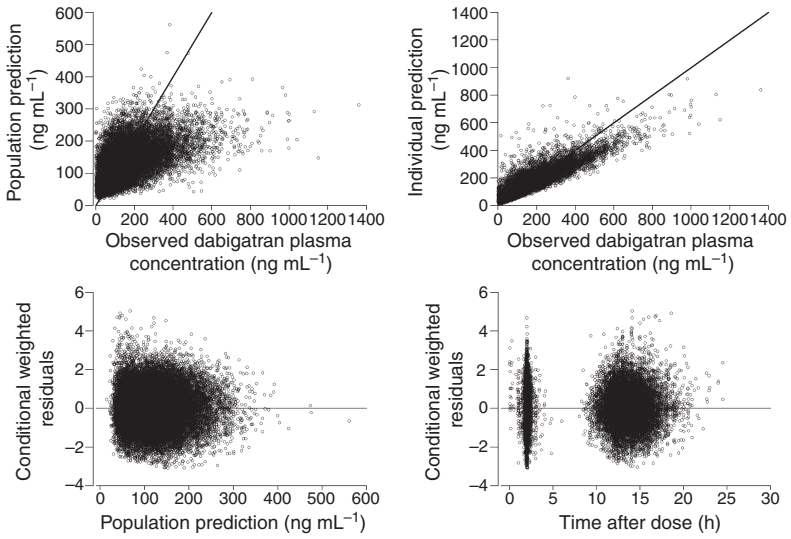

Fig. 1. Goodness-of-fit plots for the final population pharmacokinetic model. Population prediction (upper left) and individual prediction (upper right) vs. observed plasma concentrations. Solid lines indicate lines of identity. Conditional weighted residuals vs. population prediction (lower left) and time after dose (lower right).

both doses (Fig. 3). An alternative dosing regimen was simulated for the treatment of patients with severe renal impairment (CRCL 15–30 mL min^{-1}) (Fig. 4). This regimen resulted in exposure values that are well within the variability of a typical patient, except for the trough levels of patients with CRCL of only 15 mL min^{-1}.

The effect of a 6-h delay in drug intake on the plasma concentration–time profile of dabigatran is shown in Fig. 5. Except for the trough level of the delayed dosing interval, the plasma profile of the delayed administration is well within the variability of a typical patient, thus demonstrating that there is no safety issue after the subsequent regular dose.

Discussion

A popPK model was successfully developed for patients of the RE-LY trial. The large sample size and broad distribution of the covariates allowed precise characterization of the pharma-

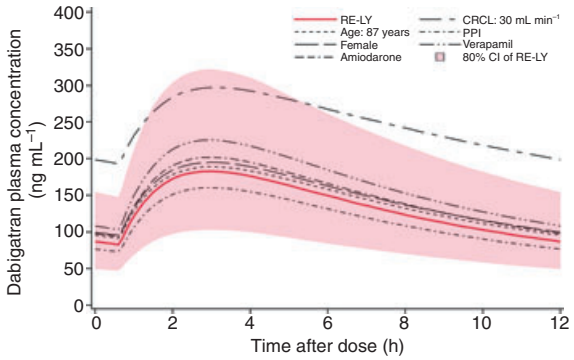

Fig. 2. Simulated median plasma concentration–time profiles at steady state for 150 mg dabigatran etexilate twice daily in various subgroups of patients. The median (solid line) and 10th and 90th percentiles (shaded area) define the reference range of a typical male RE-LY patient (male; age, 72 years; weight, 80.3 kg; creatinine clearance [CRCL], 68.64 mL min^{-1}; hemoglobin, 14.3 g dL^{-1}; not of South Asian ethnicity; no heart failure [HF] or NYHA class I HF; no comedication taken). Covariates were set to the median value or were not included, e.g. in the case of comedications. CI, confidence interval; PPI, proton-pump inhibitor.

cokinetics in the target population and a comprehensive assessment of the effects of the covariates. The covariates ethnicity (with the exception of South Asian), HF class I, left ventricular dysfunction and coadministration of diltiazem, clopidogrel and H_2 receptor blockers had no statistically significant effect on the pharmacokinetics of dabigatran. The precision and small magnitudes of the estimated effects allow the conclusion of no clinical relevance for these covariates (Figs S1–S3).

The effect of renal function on the elimination of dabigatran is well characterized [7], and expected for a drug that is mainly eliminated via the kidney. The simulations showed that, of the statistically significant effects, renal function has the most important effect on plasma concentrations, and that the effect of CRCL on $C_{pre,ss}$ is clearly non-linear. A decrease in renal clearance from 100 to 80 mL min^{-1} results in an 11% increase in systemic exposure, whereas a further 20 mL min^{-1} decrease from 50 to 30 mL min^{-1} increases exposure by 50%. From these values, the wide range of the effect even within one renal status group is evident. Furthermore, the simulations provided useful information on potential treatment with DE for severely renally impaired patients, who have not so far been systematically investigated in the clinical program.

In addition to CRCL, age and sex were both found to affect CL/F. The finding for age might be attributable to an effect separate from the decline in renal function with age. However, the age and sex effects are only minor, and are considered not to be clinically relevant for dabigatran. The additive effect of

Table 5 Parameter estimates from the final population pharmacokinetic model

Parameter	Value	RSE (%)	Description
Fixed effects (θs)			
CL_{max}/F (L h^{-1})	124	0.70	Maximum clearance
V_2/F (L)	673	0.98	Volume distribution of central compartment
Q/F (L h^{-1})	35.5*	–	Intercompartmental clearance
V_3/F (L)	345*	–	Volume distribution of peripheral compartment
K_A (h^{-1})	0.754*	–	First-order absorption rate constant
ALAG (h)	0.634*	–	Absorption lag time
F	1.00*	–	Relative bioavailability
EC_{50CRCL}[†] (mL min^{-1})	56.7*	–	CRCL value at which half of the maximum clearance is reached[‡]
$POWER_{CRCL}$[†]	1.29	2.61	Power coefficient of the E_{max} CRCL-CL/F relationship[‡]
AGE[†] (% $year^{-1}$)	−0.41	−13.07	Effect of age on CL/F[‡]
WT[§] (% kg^{-1})	0.77	5.28	Effect of weight on V_2/F[‡]
ETHN[†]	0.797	2.50	Coefficient for South Asian ethnicity on CL/F[‡]
HF[†]	0.933	0.87	Coefficient for HF classes II + III + IV on CL/F[‡]
HGB[§] (% dL g^{-1})	−3.99	−10.20	Effect of hemoglobin on V_2/F[‡]
SEX[†]	0.917	0.83	Coefficient of female patients on CL/F[‡]
PPI[¶]	0.875	1.55	Coefficient for coadministration of PPIs on F[‡]
AMIO[¶]	1.12	1.69	Coefficient for coadministration of amiodarone on F[‡]
VERA[¶]	1.23	2.20	Coefficient for coadministration of verapamil on F[‡]
Random effects: interindividual variability (IIV)			
IIV V_2/F (CV%)	20.5	13.21	IIV in the apparent volume distribution of central compartment
IIV F (CV%)	44.3	2.17	IIV in the relative bioavailability
Random effects: residual variability			
PRV (CV%)	32.8	1.02	Proportional residual variability
ARV (± SD)	6.68	7.81	Additive residual variability

CRCL, creatinine clearance; HF, heart failure; PPI, proton-pump inhibitor; RSE, relative standard error; SD, standard deviation.*Parameters fixed. [†]$CL/F = \theta_{CLmax} \times CRCL^{**}\theta_{POWERCRCL}/(\theta_{EC50CRCL}^{**}\theta_{POWERCRCL} + CRCL^{**}\theta_{POWERCRCL}) \times (1 + \theta_{AGE} * [AGE\text{-}72]) \times \theta_{ETHN} \times \theta_{HF} \times \theta_{SEX}$. [‡]For a description of the effect, see Table 4. [§]$V_2/F = \theta_{V2} \times (1 + \theta_{WT} \times [WT\text{-}80.3]) \times (1 + \theta_{HGB} \times [HGB\text{-}14.3]) \times EXP(\eta_{V2})$. [¶]$F = \theta_F \times \theta_{PPI} \times \theta_{AMIO} \times \theta_{VERA} \times EXP(\eta_F)$.

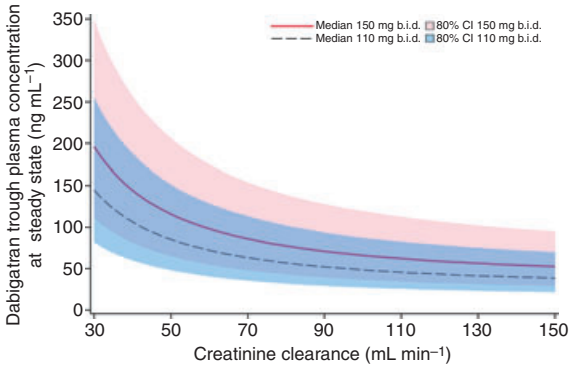

Fig. 3. Dependence of steady-state trough plasma concentrations on creatinine clearance for a typical male atrial fibrillation patient after dosing with 110 and 150 mg dabigatran etexilate twice daily (b.i.d.). Shaded areas are the 80% prediction intervals (10th to 90th percentiles). Other covariates were set to the median value or were not included, e.g. in the case of comedications. CI, confidence interval.

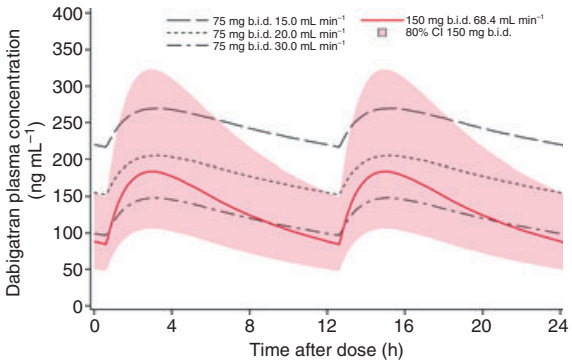

Fig. 4. Simulated median steady-state plasma concentration–time profiles of dabigatran etexilate twice daily (b.i.d.) in defined subgroups of renally impaired patients. The median (solid line) and 10th and 90th percentiles (shaded area) define the reference range of a typical male RE-LY patient (creatinine clearance [CRCL], 68.64 mL min^{-1}) for 150 mg b.i.d. Patients with severe renal impairment (CRCL, 15–30 mL min^{-1}) received 75 mg b.i.d. CI, confidence interval.

renal clearance, age and sex was also found for factor Xa inhibitors [13,14].

Among the 11 ethnic groups investigated, only patients of South Asian ethnicity, defined as individuals from India, Sri Lanka, Pakistan, and Bangladesh, were found to have CL/F that differed significantly from the population median. CL/F in those patients was decreased by 20.3% as compared with other ethnicities. An effect of this magnitude is not expected to be of clinical relevance. Additional investigations showed that the ethnicity effect is independent of body weight. Whether this is an artefact or is attributable to factors such as differences in genetics or environmental conditions remains unclear. The non-significant effects in other ethnic groups were conclusive for representative population sizes ($> 0.2\%$).

Patients with HF of NYHA classes II to IV showed a 6.7% decreased CL/F as compared with patients with no or only mild HF of class I. In the full model, a clear trend for higher effects with increased HF class except for the small class IV

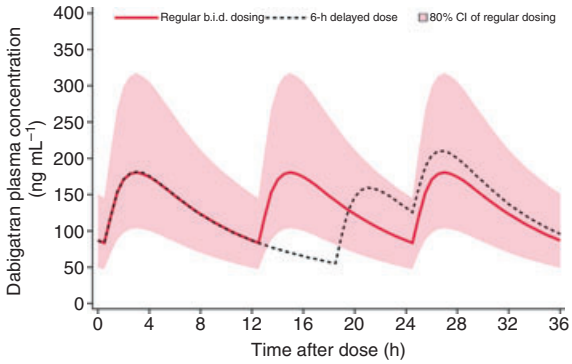

Fig. 5. Simulated median plasma concentration–time profiles at steady-state for 150 mg dabigatran etexilate twice daily (b.i.d.) with normal and 6-h delayed dosing. The median (solid line) and 10th and 90th percentiles (shaded area) define the reference range of a typical male RE-LY patient. CI, confidence interval.

(0.58%) was observed. Nevertheless, the differences between these levels of severity were not statistically significant. This finding is physiologically plausible, because cardiac output declines with advancing HF. The overall effect on exposure is minor, and is therefore regarded as not clinically relevant.

The body weight and hemoglobin concentrations of AF patients were found to affect V_2/F. Simulations (not shown) revealed that the effects have only a minor influence on the concentration–time profiles and no impact on the overall exposure. The weight effect is plausible, because of the positive correlation between body weight and volume of distribution [15]. The hemoglobin effect was also observed in previous analyses (not shown), and might be explained by desiccation, which reduces total body water and consequently results in an increase in the hemoglobin concentration.

Concerning P-GP inhibitors, the analysis focused on the effects of verapamil, amiodarone, or diltiazem, each given alone, as compared with no P-GP inhibitors. Coadministration of verapamil and amiodarone increased the bioavailability/steady-state exposure by 23% and 12%, respectively. Diltiazem did not show a statistically significant effect on F, even though 8.4% of observations were made with diltiazem cotreatment. This might be explained by the lower inhibitory potency of diltiazem for P-GP. The effect of P-GP inhibitors other than verapamil, amiodarone or diltiazem on F was found to be not statistically significant. This could be explained by the low potency of the remaining P-GP inhibitors in this group.

Coadministration of PPI decreased the bioavailability/steady-state exposure by 12.5%. This result is similar to the finding of a recent analysis (C. Dansirikul, T. Lehr, K.-H. Liesenfeld, A. Staab, S. Haertter, submitted). As with the effect of coadministration of PPI, all covariates that could be investigated in both analyses showed similar results.

In summary, the final model provides a good description of the RE-LY data. Parameter estimates for the structural model and the covariate effects could be determined with high precision (RSE $< 13.1\%$), owing to the large sample

size. The pharmacokinetics of dabigatran in AF patients could be best described by a two-compartment disposition model with a first-order absorption and a lag time. All intrinsic and extrinsic factors investigated, except for renal status, showed small to moderate effects (< 26% change in AUC_{ss}), suggesting that there is no need for dose adjustment in the following subgroups of patients: the elderly, patients with very high or low body weight, patients of South Asian ethnicity, patients with increased or decreased hemoglobin levels, and patients with HF of classes II–IV. Also, comedication, such as with PPIs or P-GP inhibitors, seems to exert only minor effects in a real-life clinical setting. In the case of renal impairment, simulations provided useful information about the potential use of DE in severely renally impaired patients. However, it needs to be emphasized that these simulations focused on dabigatran exposure but cannot consider any potentially deviating responsiveness to dabigatran in this patient population. The analysis presented will aid further optimization of therapy for patients treated with dabigatran.

Addendum

K.-H. Liesenfeld and T. Lehr: data analysis design, data analysis, interpretation of data and results, manuscript drafting, and final approval; C. Dansirikul: interpretation of data and results, manuscript drafting, and final approval; S. Haertter and A. Staab: data analysis design, interpretation of data and results, manuscript drafting, and final approval; P. A. Reilly, S. J. Connolly, M. D. Ezekowitz, S. Yusuf, and L. Wallentin: study design, data acquisition, critical review of the manuscript for important intellectual content, and final approval.

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Disclosure of Conflict of Interests

The authors, except for S. H. Connolly, M. D. Ezekowitz, S. Yusuf and L. Wallentin, are employees of Boehringer Ingelheim. S. H. Connolly, M. D. Ezekowitz, S. Yusuf and L. Wallentin report receiving consulting fees, lecture fees and grant support from Boehringer Ingelheim.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Covariate effects on apparent oral clearance (full covariate model).
Figure S2. Covariate effects on apparent volume of distribution in the central compartment (full covariate model).
Figure S3. Covariate effects on relative bioavailability (full covariate model).
Table S1. QPC results – median observed and predicted dose normalized trough concentration at steady state (stratified by dose groups and covariates).

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