Anticoagulant Effects of Dabigatran on Coagulation Laboratory Parameters in Pediatric Patients: Combined Data from Five Pediatric Clinical Trials

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Abstract

Background Dabigatran etexilate, a direct oral thrombin inhibitor, is approved to treat venous thromboembolism (VTE) in both adults and children.

Objectives This population analysis characterized relationships between dabigatran total plasma concentrations and coagulation laboratory parameters (activated partial thromboplastin time [aPTT]; diluted thrombin time [dTT]; ecarin clotting time [ECT]).

Methods Data from three phase 2a and one single-arm and one randomized, comparative phase 2b/3 pediatric studies (measurements: aPTT 2,925 [$N = 358$]; dTT 2,348 [$N = 324$]; ECT 2,929 [$N = 357$]) were compared with adult data (5,740 aPTT, 3,472 dTT, 3,817 ECT measurements; $N = 1{,}978$). Population models were fitted using nonlinear mixed-effects modeling. Covariates (e.g., sex, age) were assessed on baseline and drug-effect parameters, using a stepwise covariate model-building procedure.

Results Overall, relationships between dabigatran, aPTT, dTT, and ECT were similar in children and adults. For children aged <6 months, a higher proportion of baseline

Keywords
- dabigatran
- pediatric
- venous thromboembolism

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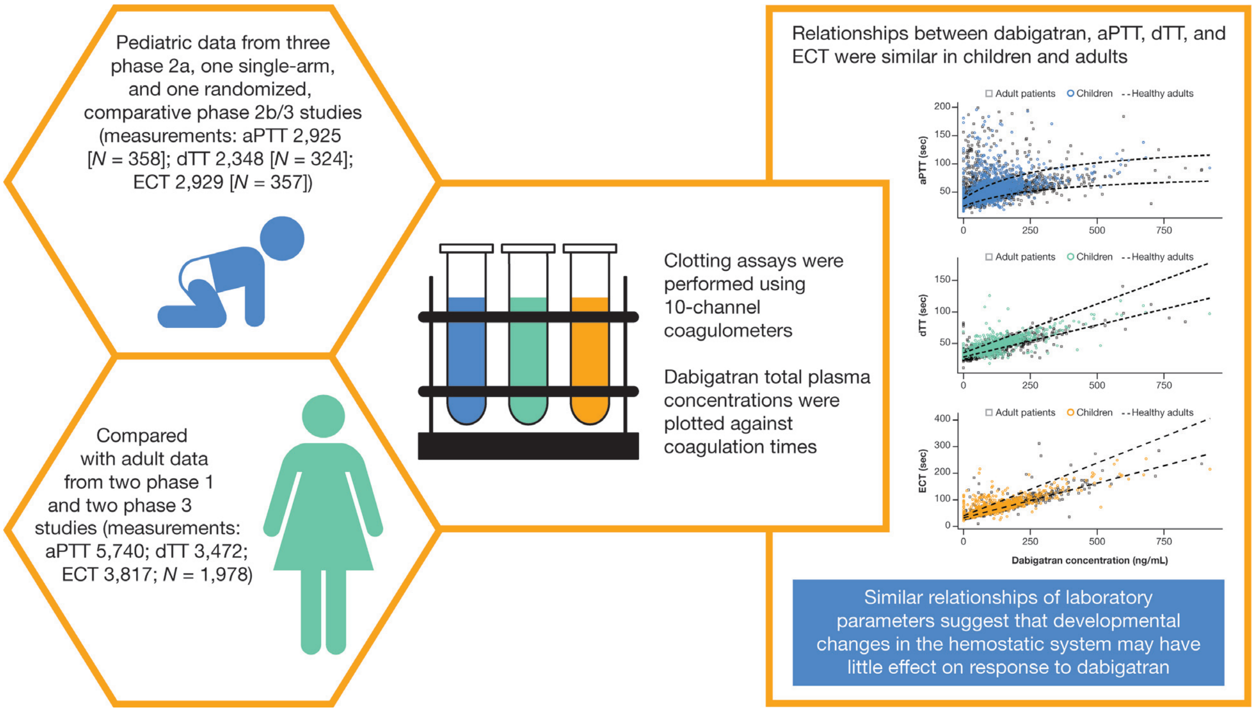

Pediatric data from three phase 2a, one single-arm, and one randomized, comparative phase 2b/3 studies (measurements: aPTT 2,925 [*N* = 358]; dTT 2,348 [*N* = 324]; ECT 2,929 [*N* = 357])

Compared with adult data from two phase 1 and two phase 3 studies (measurements: aPTT 5,740; dTT 3,472; ECT 3,817; *N* = 1,978)

Clotting assays were performed using 10-channel coagulometers

Dabigatran total plasma concentrations were plotted against coagulation times

Relationships between dabigatran, aPTT, dTT, and ECT were similar in children and adults

Similar relationships of laboratory parameters suggest that developmental changes in the hemostatic system may have little effect on response to dabigatran

Visual Summary Effects of dabigatran on coagulation parameters in children.

samples were outside or close to the upper aPTT and ECT adult ranges. No age-related differences were detected for dTT. With increasing dabigatran concentration, aPTT rose nonlinearly (half the maximum effect at 368 ng/mL dabigatran) while dTT and ECT increased linearly (0.37 and 0.73% change per ng/mL dabigatran, respectively). Mean baseline aPTT (45 vs. 36 seconds) and ECT (40 vs. 36 seconds) were slightly increased for those aged <6 months versus older children.

Conclusion The similar relationships of laboratory parameters observed across pediatric age groups suggests that developmental changes in the hemostatic system may have little effect on response to dabigatran.

Introduction

There has been a notable increase in the incidence of acute venous thromboembolism (VTE) in children over the past 25 years, due to raised clinician awareness, medical advances in supportive care and the use of central lines, and refinements in imaging techniques increasing the diagnosis of VTE.[1,2] However, the treatment of children with acute VTE is challenging for clinicians. Standard of care (SOC) treatment for acute VTE in children is extrapolated from adult VTE data, and comprises unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), or vitamin K antagonists (VKAs) such as warfarin.[3] There are limitations with SOC treatment; for example, UFH and LMWH have no oral formulations, depend upon antithrombin levels, require frequent monitoring, and can cause heparin-induced thrombocytopenia; in addition, UFH has variable pharmacokinetics (PK).[3,4] VKAs also have variable PK, require frequent monitoring, and have multiple food and drug interactions.[5] Physiological age-related changes in the hemostatic and coagulation systems can result in differing responses of coagulation assays to SOC according to age.[6,7] In fact, some coagulation assays, including activated partial thromboplastin time (aPTT) and thrombin clotting time, have limitations that preclude a complete reflection of the UFH anticoagulant levels achieved, particularly in very young patients.[8] For example, if children requiring SOC also have decreased antithrombin levels, heparin levels can be underestimated[9]; conversely, administering antithrombin without decreasing the dose of heparin may increase the risk of bleeding in these patients.

Dabigatran etexilate, a thrombin direct inhibitor, is approved in both adults and children for the treatment of acute VTE and the prevention of recurrent VTE, based upon pivotal clinical study data.[10–14] Direct oral anticoagulants, such as dabigatran etexilate, offer different treatment options for VTE. Dabigatran can overcome some of the limitations associated with SOC, as it does not require frequent monitoring and has fewer drug interactions,[15] nor does it rely upon antithrombin levels. In a previous analysis of 35 children aged from birth to <18 years, the relationships between dabigatran concentrations and aPTT, ecarin clotting time (ECT), and diluted thrombin time (dTT) were similar across most age groups compared with adults.[16] Based on this preliminary analysis, the relationship for dabigatran and aPTT was best described using a maximum effect (E_{max}) model, while dTT and ECT were best described using linear relationships (slope–intercept models).[16] Comparable dabigatran relationships for these laboratory coagulation parameters in children across age groups suggests that developmental hemostatic changes may have little impact on dabigatran. Similar dabigatran relationships between children and adults for these laboratory coagulation parameters suggest that clinical responses to dabigatran in children may be comparable to those seen in adults.

The current submission reflects a much larger sample size with a more representative and rich dataset encompassing the entire dabigatran pediatric clinical trial program, including the phase 2b/3 trials. The aim of this analysis was to characterize the relationship between dabigatran plasma concentrations and laboratory coagulation parameters (aPTT, dTT, and ECT) across different age groups in children, including a visual comparison to adult data.

Methods

Data Sources

Data generated from five distinct pediatric VTE studies (►**Supplementary Table S1**, available in the online version) were analyzed; four evaluated dabigatran etexilate (capsules, and child-friendly pellets and oral solution) when administered according to an age- and weight-based dosing algorithm, and one administered weight-adjusted capsules. Three were phase 2a studies; NCT02223260 (eight infants aged from birth to <1 year), NCT01083732 (18 children aged 1 to <12 years), and NCT00844415 (nine adolescents aged 12 to <18 years).[17–19] Two were phase 2b/3 studies; DIVERSITY, NCT01895777[11] (data from 176 treated children aged from birth to <18 years), and NCT02197416[10] (data from 213 children aged from 3 months to <18 years). The studies were single-arm except for DIVERSITY, which was an open-label, randomized, noninferiority study. They were conducted between August 2009 and November 2019. Adult model predictions of dabigatran concentration–response for aPTT, dTT, and ECT, respectively, were based upon dabigatran and laboratory coagulation parameter data from two randomized, double-blind phase 1 and two randomized, double-blind phase 3 studies conducted between April 2006 and August 2014 (see **Supplementary Material: Adult Data Sources** for more detail [available in the online version]). Briefly, two were phase 1 idarucizumab studies that evaluated dabigatran (NCT01688830, data from 51 healthy adult males aged 18–45 years; and NCT01955720, data from 46 males aged 45–80 years),[20,21] and two were phase 3 dabigatran studies, namely RE-COVER II (NCT00291330, data from 1,179 dabigatran-treated adults) and RE-NOVATE (NCT00657150, data from 702 dabigatran-treated adults).[13,22] All trials were conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice, and were approved by all investigational site ethics committees. For PK assessments, plasma concentrations of total dabigatran (after alkaline cleavage of glucuronide conjugates) were obtained by high-performance liquid chromatography (HPLC) tandem mass spectrometry. Assays for three laboratory coagulation parameters (aPTT, dTT, and ECT) have been previously described (see **Supplementary Material: Clotting Assays** for more detail [available in the online version]).[16]

Exploratory Graphical Analysis

Pooled pediatric data (overall and by age group) were used to generate graphs showing dabigatran total plasma concentrations against coagulation times (absolute clotting times and relative change from baseline [pretreatment value]). Stratifications considered included age group and study. Graphs were compared with observed data from adults with VTE, as well as model predictions for healthy adult subjects.

Modeling Analysis

The previously described pediatric models[16] were the basis for this larger pooled analysis, and were refined if graphical analyses indicated any misspecification (see **Supplementary Material: Population Model Development** for more detail [available in the online version]). Linear and nonlinear concentration–laboratory coagulation time models were applied to pediatric and adult datasets to estimate parameters including interindividual variability. Covariates (sex and age) were assessed on baseline and drug-effect parameters, using a stepwise covariate model-building (SCM) procedure (see **Supplementary Material: Population Model Development** for more detail [available in the online version]). Interindividual variability parameters supported in the base model further refined the SCM and finalized the model. Model evaluation was guided by numerical criteria (e.g., objective function value, condition number, relative standard errors, and shrinkage estimates) and basic graphical goodness-of-fit diagnostics (e.g., residual plots and plots of observed vs. predicted clotting times), including visual predictive checks (see **Supplementary Material: Population Model Development** for more detail [available in the online version]).

Software

Nonlinear mixed-effects modeling was performed using NONMEM version 7.3.0 (Icon Development Solutions, Ellicott City, Maryland, United States). Data preparation, graphical summaries, and nonparametric regressions of dabigatran concentration–laboratory coagulation time parameters against age were performed using the R statistical environment version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

►**Table 1** shows the aPTT, dTT, and ECT PK populations from the pediatric studies. Across all the pediatric studies, there

Table 1 Variables from the pediatric studies

	NCT02223260	NCT01083732	NCT00844415	DIVERSITY (NCT01895777)	NCT02197416
Treated with dabigatran, *N* Age, y	8 <1	15 1 to <12	9 12 to <18	176 Birth to <18	213 3 mo to <18
aPTT					
Number of children with aPTT data	8	15	9	171	213[a]
Number of aPTT observations	24	45	42	1,185	1,629
Age, y					
N	8	15	9	171	155
Median (range)	0.2 (0.1–0.5)	2.8 (1.2–8.5)	16.0 (13.8–18.0)	14.5 (0.1–18.1)	14.5 (0.5–18.0)
Weight, kg					
N	8	15	9	171	155
Median (range)	4.2 (3.8–7.1)	15.0 (9.0–43.0)	54.0 (47.0–84.0)	53.0 (3.7–131)	60.0 (6.0–132)
dTT					
Number of children with dTT data	8	18	9	149	197[b]
Number of dTT observations	24	55	42	958	1,269
Age, y					
N	8	18	9	149	140
Median (range)	0.2 (0.1–0.5)	4.1 (1.2–11.8)	16.0 (13.8–18.0)	13.6 (0.1–18.1)	14.7 (0.5–18.0)
Weight, kg					
N	8	18	9	149	140
Median (range)	4.2 (3.8–7.1)	16.0 (9.0–43.0)	54.0 (47.0–84.0)	52.0 (3.7–131)	60.0 (6.0–132)
ECT					
Number of children with ECT data	8	14	9	171	213[a]
Number of ECT observations	24	40	42	1,185	1,638
Age, y					
N	8	14	9	171	155
Median (range)	0.2 (0.1–0.5)	2.5 (1.2–8.5)	16.0 (13.8–18.0)	14.5 (0.1–18.1)	14.5 (0.5–18.0)
Weight, kg					
N	8	14	9	171	155
Median (range)	4.2 (3.8–7.1)	13.5 (9.0–43.0)	54.0 (47.0–84.0)	53.0 (3.7–131)	60.0 (6.0–132)

Abbreviations: aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time.

[a] Includes 58 children who rolled over from the DIVERSITY trial to the NCT02197416 trial. To avoid counting the same patient twice, data for the variables shown do not include those patients originally enrolled in the DIVERSITY trial who were rolled over to the NCT02197416 trial.

[b] Includes 57 children who rolled over from the DIVERSITY trial to the NCT02197416 trial. To avoid counting the same patient twice, data for the variables shown do not include those patients originally enrolled in the DIVERSITY trial who were rolled over to the NCT02197416 trial.

were 2,925 aPTT measurements from 358 children, 2,348 dTT measurements from 324 children, and 2,929 ECT measurements from 357 children. ►**Table 2** summarizes the populations and median baseline (range) aPTT, dTT, and ECT levels for the children according to their age group. From 1,978 adults, there were 5,740 aPTT, 3,472 dTT, and 3,817 ECT measurements available, and their median (range) baseline aPTT, dTT, and ECT levels are shown in ►**Table 3**.

Exploratory Graphical Analysis

The prior $E_{\max}$ model for aPTT and the prior linear models for dTT and ECT were all able to describe the final pediatric phase 2b/3 data with small modifications, as shown by visual predictive checks (in ►**Supplementary Fig. S1**, available in the online version). Based upon visual analysis, relationships were similar in children and adults for dabigatran concentrations across all three laboratory coagulation parameters (►**Fig. 1**). aPTT increased nonlinearly with increasing

Table 2 Variables from the pediatric studies by age group

	Age group			
	0 to <6 mo	6 mo to <2 y	2 to <12 y	12 to <18 y
aPTT				
Number of children with aPTT data	17	26	81	234
Number of aPTT observations	52	171	608	2,094
Age, y, median (range)	0.2 (0.1–0.5)	1.2 (0.5–2.0)	6.9 (2.0–12.0)	16.1 (12.0–18.1)
Weight, kg, median (range)	4.5 (3.7–7.7)	9.1 (6.0–15.0)	22.0 (10.7–54.2)	64.8 (30.0–132)
Baseline aPTT, s				
N[a]	11	26	74	210
Median (range)	41.1 (28.2–51.2)	34.6 (19.8–65.3)	34.6 (18.4–91.2)	34.2 (16.1–313)
dTT				
Number of children with dTT data	17	26	79	202
Number of dTT observations	62	170	554	1,562
Age, y, median (range)	0.2 (0.1–0.5)	1.2 (0.5–2.0)	6.6 (2.1–11.9)	16.0 (12.0–18.1)
Weight, kg, median (range)	4.4 (3.7–7.7)	9.1 (6.0–15.0)	21.9 (10.7–47.0)	65.8 (32.1–132)
Baseline dTT, s				
N[a]	10	25	61	125
Median (range)	31.8 (27.8–32.7)	32.0 (28.4–39.5)	32.2 (27.7–46.0)	32.3 (26.3–68.9)
ECT				
Number of children with ECT data	17	26	80	234
Number of ECT observations	52	172	607	2,098
Age, y, median (range)	0.2 (0.1–0.5)	1.2 (0.5–2.0)	7.0 (2.1–11.9)	16.1 (12.0–18.1)
Weight, kg, median (range)	4.5 (3.7–7.7)	9.1 (6.0–15.0)	22.2 (10.7–54.2)	64.8 (30.0–132)
Baseline ECT, s				
N[a]	11	26	72	210
Median (range)	40.3 (35.5–55.8)	35.6 (31.7–41.8)	34.3 (27.1–74.6)	34.9 (21.2–118)

Abbreviations: aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time.
[a] Baseline values were not available for some children.

dabigatran total plasma concentration, whereas dTT and ECT increased linearly with rising dabigatran total plasma concentration (►**Fig. 1**).

Minor age-related differences were detected for baseline aPTT and ECT (►**Fig. 2**). Based upon visual analysis, in children aged from birth to <6 months, there was a trend toward more aPTT and ECT samples being outside or in the upper reference range of healthy adult subjects. For dTT, no age-related differences were detected for the baseline or the slope parameters (►**Fig. 2**). There was a minor influence of age upon the drug effect parameter for ECT. Small study-related differences were detected for baseline aPTT and ECT (in ►**Supplementary Fig. S2**, available in the online version). Across all studies, the majority of dTT samples were within the healthy adult reference range. The DIVERSITY study included five neonates and young infants in the birth to <6 months group (►**Supplementary Fig. S3**, available in the online version), but as so few were included in the analysis, data interpretation for this age group is difficult. While relationships between dabigatran plasma concentration, and aPTT, dTT, and ECT were similar between Caucasian, Asian, and Black patients (data not shown), there were few Asian and Black patients compared with Caucasian patients for each laboratory coagulation parameter (►**Table 1**).

Modeling Analysis

Baseline levels for each laboratory coagulation parameter were included in the model; for aPTT, the correlation between baseline and $E_{\max}$ was –0.722, and for dTT and ECT the correlation between baseline and slope was –0.646 and –0.888, respectively. Final model predictions showed similar relationships between children and healthy adults between dabigatran plasma concentration, and aPTT, dTT, and ECT, respectively (►**Fig. 3**). Parameter estimates of the final aPTT, dTT, and ECT models are shown in ►**Supplementary Table S2** (available in the online version).

aPTT was nonlinear and best described by an $E_{\max}$ relationship (►**Fig. 3**). Mean baseline aPTT was estimated to be increased in children aged <6 months (the estimated cut-off was 5.8 months) versus older children (44.8 vs. 36.1 seconds, a 1.25-fold increase). For all children, there was a twofold increase from baseline at infinity exposure ($E_{\max}$, 2.02), with half

Table 3 Variables from the adult studies (adapted from Maas et al[16])

	Healthy adult volunteers		Adult patients	
	NCT01688830[a]	NCT01955720[a]	RE-COVER (NCT00291330)	RE-NOVATE II (NCT00657150)
Number of patients	51	46	1,179	702
Age, y, mean (range)	31 (20–45)	64 (45–76)	55 (18–93)	61 (23–87)
Dabigatran concentration[b] IQR, ng/mL	67.4–181	66.4–218	37.3–102	17.2–91.9
aPTT				
Number of observations	737	792	2,278	1,933
Baseline aPTT, s, mean (range)	33.2 (23.5–40.0)	29.7 (22.1–38.4)	–[c]	32.6 (19.6–156)
dTT				
Number of observations	739	793	–[d]	1,940
Baseline dTT, s, mean (range)	32.1 (29.4–38.1)	32.1 (29.7–38.1)	–	32.1 (11.4–82.6)
ECT				
Number of observations	739	793	2,285	–[e]
Baseline ECT, s, mean (range)	37.4 (33.6–42.5)	34.6 (30.3–38.9)	–[c]	–

Abbreviations: aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; IQR, interquartile range.
[a] Only placebo and dabigatran treatment periods were used for the current analysis.
[b] Based on plasma concentration samples across all sampling times, including samples measured at times other than trough (predose) and samples taken outside of the sampling window.
[c] Baseline measurements were not taken in the RE-COVER trial.
[d] dTT was not measured in the RE-COVER trial.
[e] ECT was not measured in the RE-NOVATE II trial.

the $E_{\max}$ occurring at 368 ng/mL dabigatran (EC_{50}, 368 ng/mL). The differences across age groups appeared to be related to baseline aPTT levels.

A linear relationship was seen for dTT and dabigatran concentration (►**Fig. 3**). The observed baseline dTT was similar between children and adults (32.1 and 31.9 seconds, respectively), and no age-related differences were identified in children. For the linear relationship between dTT and dabigatran concentration, the slope was estimated as having on average a 0.37% change in dTT per ng/mL dabigatran.

A linear relationship was also seen between ECT and dabigatran concentration (►**Fig. 3**). On average, this translated into a 0.73% change in ECT per ng/mL dabigatran for all children. For ECT, there was a small impact of age, with mean baseline ECT estimated to be increased in children <6 months of age (the estimated cut-off was 5.8 months) than in all children (39.9 vs. 36.4 seconds).

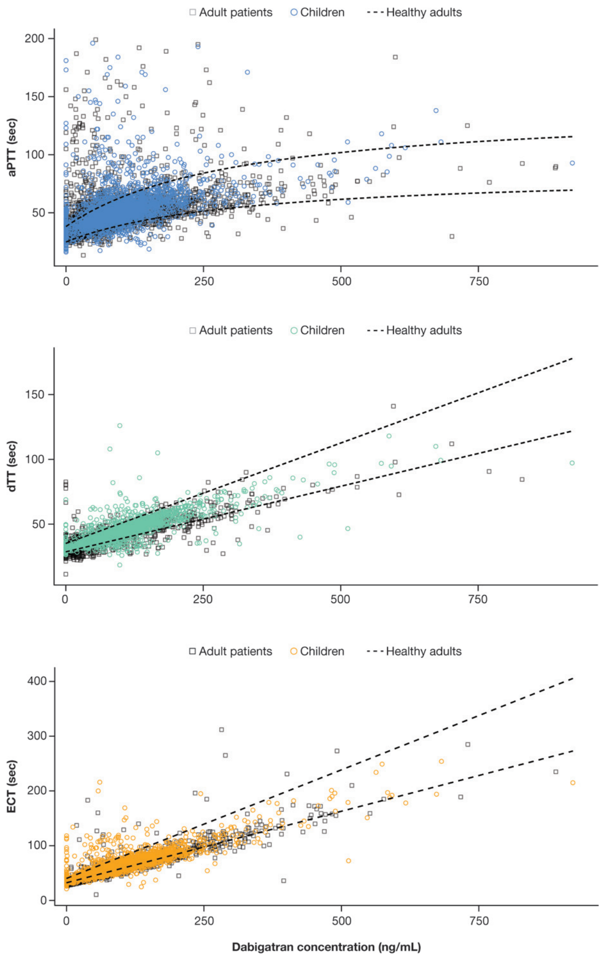

Fig. 1 Graphical visualization of the relationships between observed aPTT, dTT, and ECT, and dabigatran total plasma concentrations. In all plots, *circles* are observed data from the five pediatric studies (►**Table 1**), and the *dashed lines* represent a model-based 95% prediction interval in healthy adults. In the aPTT plot, *squares* represent 4,211 data observations from 1,881 adult patients in the RE-COVER and RE-NOVATE II studies. Measurements >200 seconds ($n = 14$) from six children, as well as 16 measurements from adult patients, are not displayed. In the dTT plots, squares represent 1,933 data observations from 702 adult patients in the RE-NOVATE II study. In the ECT plot, *squares* represent 2,285 data observations from 1,179 adult patients in the RE-COVER study. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; sec, seconds.

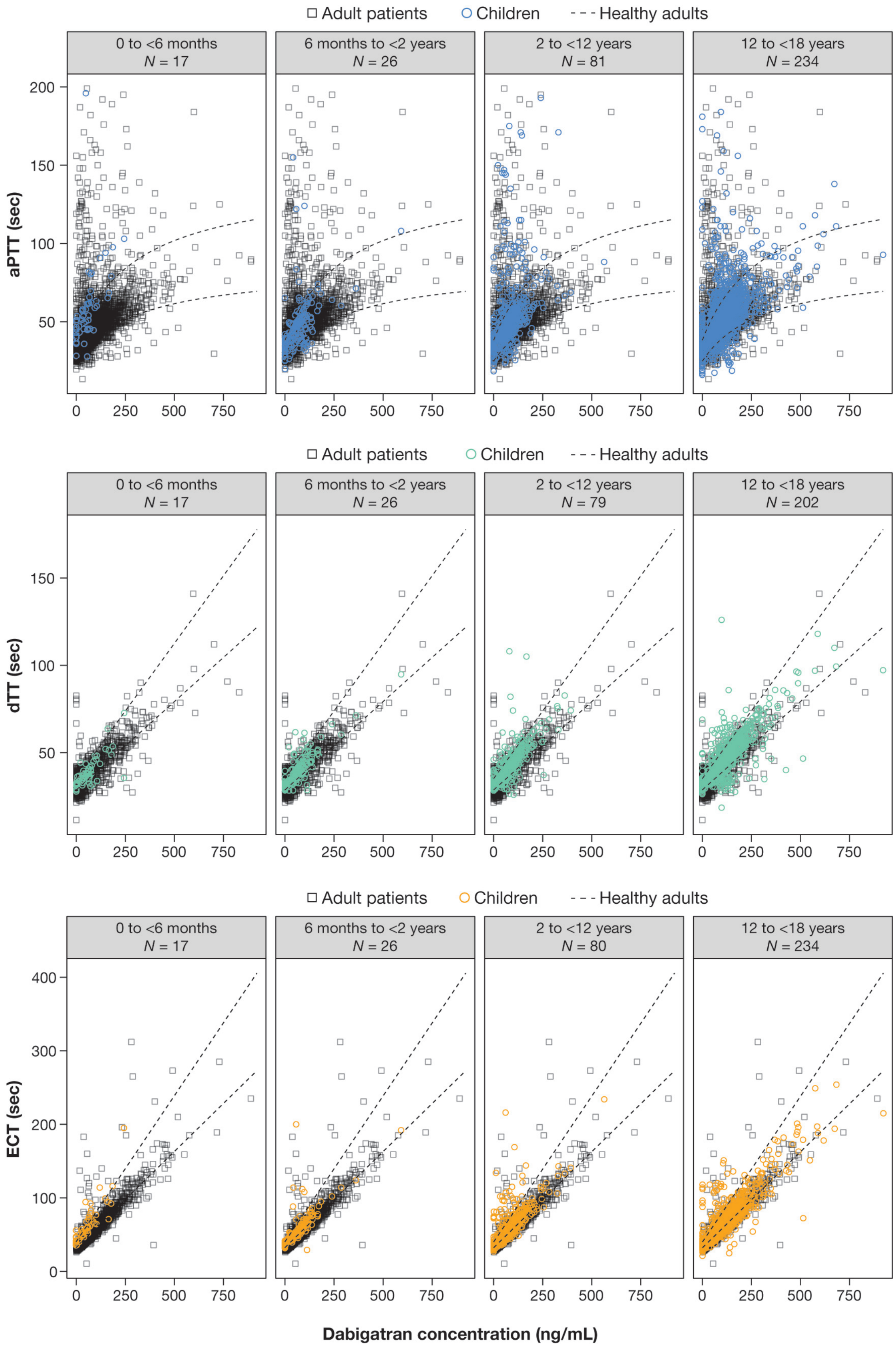

Fig. 2 Graphical visualization of the relationships between observed aPTT, dTT, and ECT, and dabigatran total plasma concentrations by pediatric age groups. In all plots, *circles* are observed data from the five pediatric studies (►**Table 1**), and the *dashed lines* represent a model-based 95% prediction interval in healthy adults. In the aPTT plot, *squares* represent 4,211 data observations from 1,881 adult patients in the RE-COVER and RE-NOVATE II studies. In the dTT plots, *squares* represent 1,933 data observations from 702 adult patients in the RE-NOVATE II study. In the ECT plot, *squares* represent 2,285 data observations from 1,179 adult patients in the RE-COVER study. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time; sec, seconds.

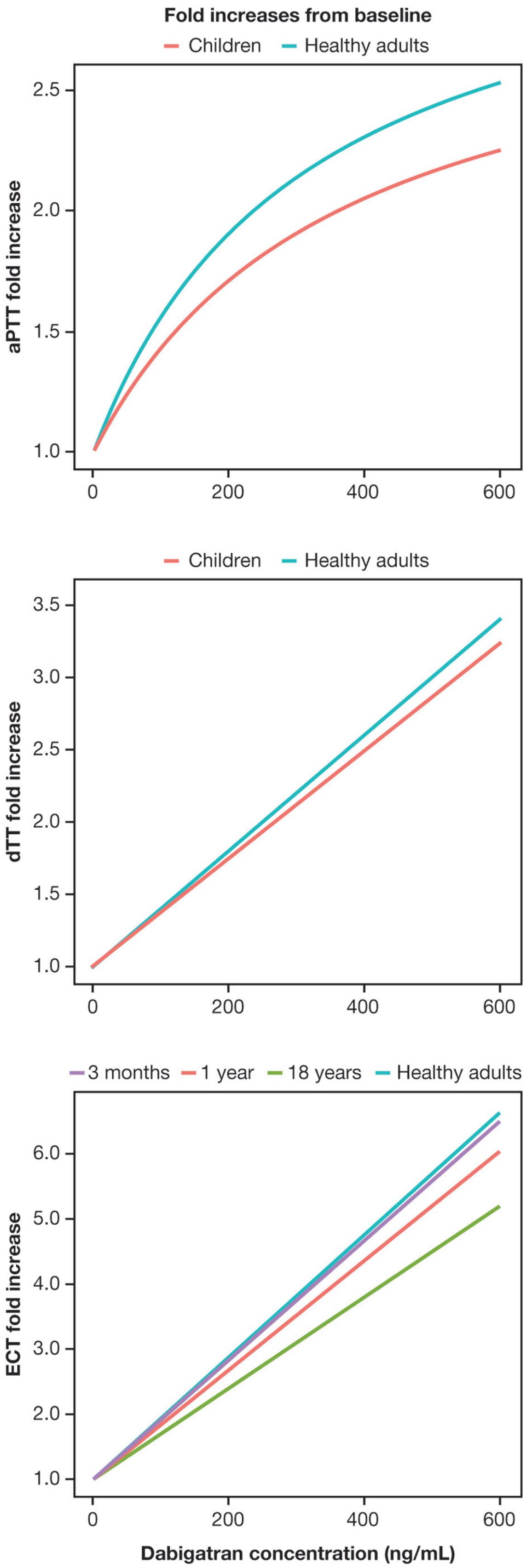

Fig. 3 Population model predictions for the final aPTT, dTT, and ECT models and dabigatran total plasma concentrations, across age groups. aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time.

Discussion

Our data on between 324 and 358 patients, and up to 3,015 data observations with each assay, represent one of the most comprehensive assessments of the response of routine hemostatic assays to anticoagulant drugs in general, and to dabigatran specifically, in a large cohort of pediatric patients, whereby the drug levels were measured using a gold standard method (HPLC). For the relationships between dabigatran and the laboratory coagulation parameters, there were either no, or small, age-related differences across pediatric age groups, and between children and adults (both healthy and/or patients), apart from baseline differences. Graphical analysis and model predictions did not identify any age-related differences for dTT. However, age-related differences were identified only for baseline aPTT and ECT clotting times. All three laboratory coagulation parameters were sensitive to dabigatran exposure. Clotting times for both parameters from children aged <6 months tended to lie outside or in the upper healthy adult reference range, and modeling estimated both to be increased in children aged <6 months versus older children. Increased baseline clotting times are expected because of the well-known normal developmental hemostasis in the first 6 months of life, whereby several key hemostatic components are reduced in infants <6 months compared with adults.[23] Model predictions showed similar relationships between children and healthy adults for dabigatran concentrations, and aPTT, dTT, and ECT, respectively, across all pediatric age groups. These findings support targeting similar exposure levels to adults for pediatric dosing.

Age is a major factor in determining the dosing of anticoagulants, with increased doses required in younger children.[24,25] PK modeling demonstrated that younger children cleared LMWH more rapidly and therefore required a higher initial dose.[25] In contrast, as renal function is immature in children <2 years old,[26] lower doses are required for dabigatran due to reduced renal clearance. Furthermore, age-related differences in responses using several different coagulation assays (e.g., anti-FXa, anti-FIIa, protamine titration, and thrombin generation assays) are well documented for SOC treatment.[6,7] In a previous dabigatran population analysis comprising 35 children, Maas et al noted that those aged <1 year had slightly increased aPTT and ECT in comparison to adults using graphical analysis, with modeling analysis suggesting a slight increase in ECT and aPTT in those aged <2 months, relative to adults.[16] In our larger analysis, age-related differences in the relationships between dabigatran concentration, and aPTT, dTT, and ECT, respectively, were very small, both between children and adults, and across pediatric age groups; moreover, modeling showed increased mean baseline aPTT and ECT in those children aged <6 months compared with all children. However, there was substantial variability in baseline aPTT and ECT, and so our view is that as long as children are prescribed dabigatran etexilate according to its age- and weight-based dosing algorithm, they should achieve comparable exposure levels to adults. Indeed, a separate dabigatran etexilate population PK simulation analysis of the same pediatric population showed that monitoring dabigatran levels is not required when dabigatran is dosed according to its age- and weight-based dosing algorithm.[27] Additionally, phase 2b/3 clinical data have shown the efficacy and safety of dabigatran in children when dosed using the age- and weight-based dosing algorithm.[10,11] As the effects of dabigatran are mostly dependent on kidney function, and vary according to kidney maturation in pediatric patients, weight-based dosing without consideration of age is not appropriate for evaluation of dabigatran plasma concentrations and coagulation parameters,[27] and was therefore not assessed in this study.

In vitro data using pooled plasma from 41 healthy children (age groups comprised <1 year, 1 to <5 years, 5 to <10 years, and 10 to <17 years) and 20 adults reported consistent results with dTT assays for increasing dabigatran concentrations across all pediatric age groups.[28] In the previous population analysis of dabigatran reported by Maas et al (122 observations), concentration–dTT relationships were consistent in children across all ages and adults.[16] In this more robust analysis of 2,348 dTT measurements from 324 children, there was less unexplained variability and less between-patient variability in dTT for dabigatran compared with aPTT and ECT. Results indicate that dTT has a linear relationship to dabigatran in concentrations >50 ng/mL. However, all three laboratory coagulation parameters showed similar relationships to dabigatran concentrations between children and adults. Dabigatran has already been shown to be a safe and effective treatment for acute VTE and secondary prevention of VTE in children, without the need for monitoring,[10,11] but in emergencies when dabigatran levels need to be determined for patient care, dTT analysis would be preferred as it is insensitive to the age-related differences in the hemostatic system.

Adult trials conducted on a large number of patients (e.g., RE-LY in >18,000 patients[29] and RE-COVER in >2,500 patients[13]) failed to demonstrate any correlation between clinical outcomes and clotting assays. As we found similarities of clotting assays in pediatric and adult populations treated with dabigatran etexilate, we would not anticipate finding any correlations between clinical outcomes and clotting assays in the pediatric study population.

There are both strengths and limitations with this dabigatran population analysis, which included well-controlled clinical studies, albeit with different study designs and patient populations. However, while relationships between dabigatran concentrations were analyzed for aPTT, dTT, and ECT, not all studies included in this analysis used all of these coagulation assays (e.g., the RE-COVER trial did not evaluate dTT and RE-NOVATE II did not evaluate ECT). Further, the same aPTT, dTT, and ECT reagents and hemostasis analyzers were used for the results presented here and the findings are most likely not directly generalizable to correlations with other aPTT/dTT/ECT reagents and instruments. Unsurprisingly, as there were few very young children ($n = 17$ aged <6 months, including five neonates and young infants [see ►**Supplementary Table S1** footnote, available in the online version]), data interpretation is difficult for this age group; therefore, physicians should be more vigilant when targeting dabigatran exposure in this age group.

This study aimed to characterize the relationship between dabigatran plasma concentrations and laboratory coagulation parameters (aPTT, dTT, and ECT) across different age groups in children, including a visual comparison to adult data. Apart from baseline differences, we found only very small age-related differences across different pediatric age groups, and between children and adults (both healthy and/or patients) in coagulation parameters; however, due to the limited data in children aged <6 months, caution should be observed when interpreting data for this age group. Based on this analysis and clinical data showing the efficacy and safety of dabigatran in the pediatric VTE setting,[10,11] the use of an age- and weight-adjusted dabigatran dosing algorithm to target adult dabigatran exposure is appropriate in children with VTE. Notably, we found dTT to be the most reliable method of determining dabigatran concentrations.

What is known about this topic?

- Dabigatran etexilate is approved in adults and children for acute venous thromboembolism (VTE) and the prevention of recurrent VTE.
- Dabigatran has fewer limitations than standard of care anticoagulants as it does not require frequent monitoring, has fewer drug interactions, and does not rely upon antithrombin levels.
- In a small sample size of 35 children, the relationships between dabigatran concentrations and activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and diluted thrombin time (dTT) were similar to adults, suggesting that clinical responses to dabigatran in children may be comparable to those seen in adults.

What does this paper add?

- This study reports the results from an analysis of 358 children participating in five clinical trials and 1,978 adults, comparing aPTT, dTT, and ECT data.
- Characterization of the relationship between dabigatran plasma concentrations and laboratory coagulation parameters (aPTT; dTT; ECT) across different age groups suggests that developmental changes in the hemostatic system may have little effect on response to dabigatran.
- In certain clinical situations where health care providers need to know an approximate dabigatran plasma level for safety procedures, overdoses, or compliance, that, in children over all ages, the dTT and ECT are linear over concentrations between 50 and 250 ng/mL, the recommended assay is the dTT.

Author Contributions

L.G.M., D.R., F.H., and D.J., contributed to the concept, design, and analysis of the data. All authors contributed

to critical writing or revising of intellectual content and final approval of the version to be published.

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Data Sharing Statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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Conflict of Interest

L.G.M. is a member of a pediatric expert working group for Boehringer Ingelheim and has received a research grant from Bristol Myers Squibb. D.R. is an employee of Pharmetheus, contracted as an external consultant by Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals. F.H., D.J., I.T., S.G., and M.B. are all employees of Boehringer Ingelheim. M.A. is a member of a pediatric expert working group for Boehringer Ingelheim and has received advisory board fees from Daiichi Sankyo. L.R.B. is a member of a pediatric expert working group for Boehringer Ingelheim and has received advisory board fees from Boehringer Ingelheim. L.B. is a member of a pediatric expert working group for Boehringer Ingelheim, and reports fees to her institution from Janssen Pharmaceuticals. E.C. is a member of a pediatric expert working group for Boehringer Ingelheim, and reports personal fees from Roche, Sobi, Bristol Myers Squibb, CSL Behring, and Shire/Takeda. J.H. is a member of a pediatric expert working group for Boehringer Ingelheim and has received honoraria from Boehringer Ingelheim for congress presentation. M.L. is a member of a pediatric expert working group for Boehringer Ingelheim.

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