Anticoagulant Effects of DOACs in Children: Coagulation Assay Responses

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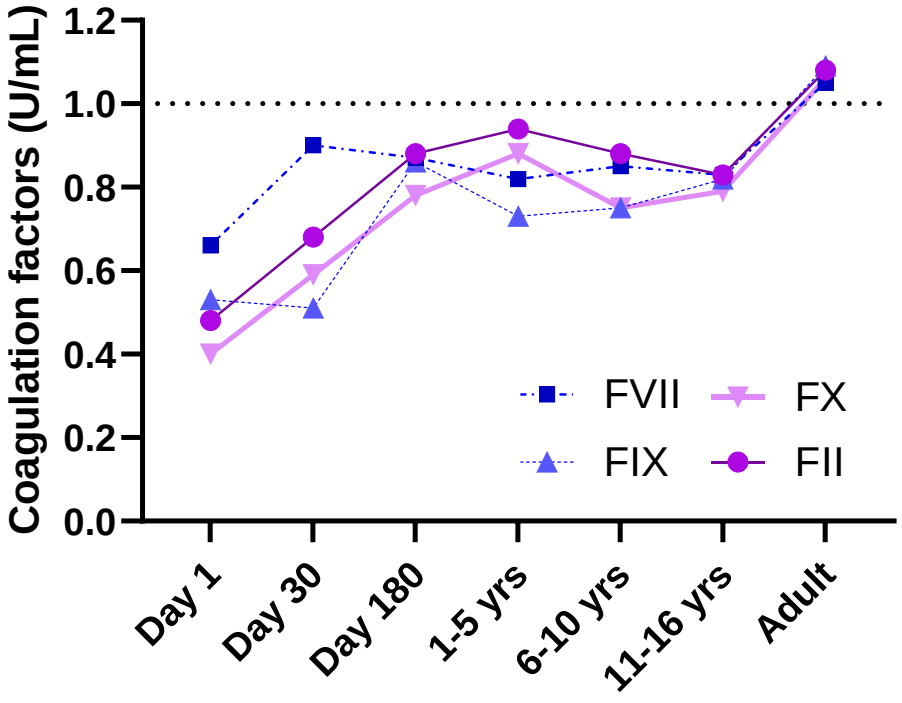
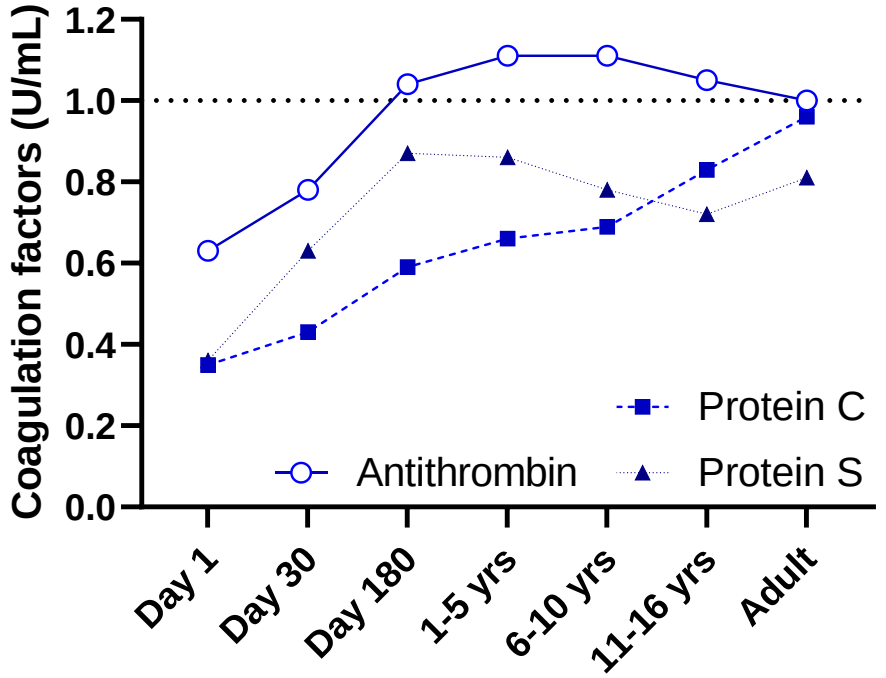
Developmental hemostasis: the normal physiological childhood hemostatic system whereby hemostatic proteins are lower at birth in comparison to adults and increase with age





Developmental hemostasis may result in differences in the correlation of standard anticoagulant concentrations to routine laboratory tests over childhood

Figures adapted from Andrew et al. Blood 1987;70:165 and Andrew et al. Blood 1992;80:1998. F, Factor
Kuhle et al. Haematologica 2007;92:554; Mitchell, Vegh. Klin Padiatr 2010;222:164

Heparin inhibits multiple activated coagulation factors

Heparin potentiates the inhibitory effects of antithrombin on thrombin and Factor Xa (primary anticoagulant effect) and also acts on Factors IXa, XIa, and XIIa

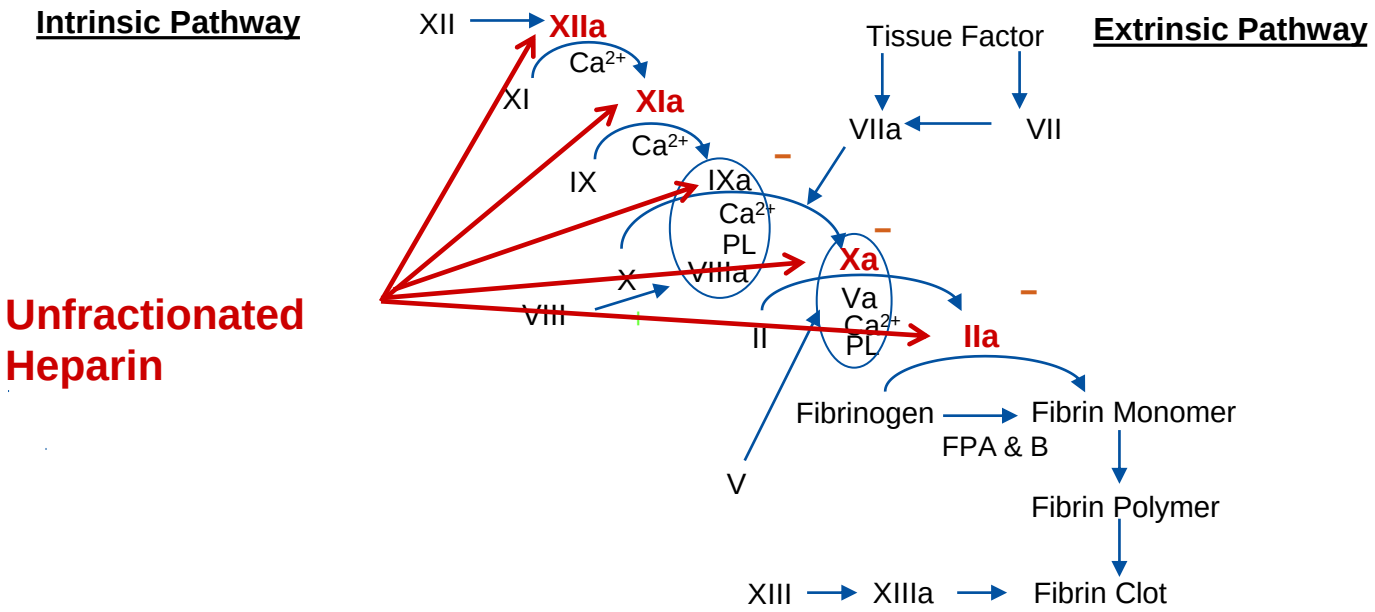


Figure prepared by L. Mitchell

FPA, fibrinopeptide A; FPB, fibrinopeptide B; PL, phospholipid

Young. Hematology Am Soc Hematol Educ Program 2015;2015:111

The aPTT assesses the heparin effect on the Intrinsic Pathway and is sensitive to variation of levels of all Intrinsic Pathway factors

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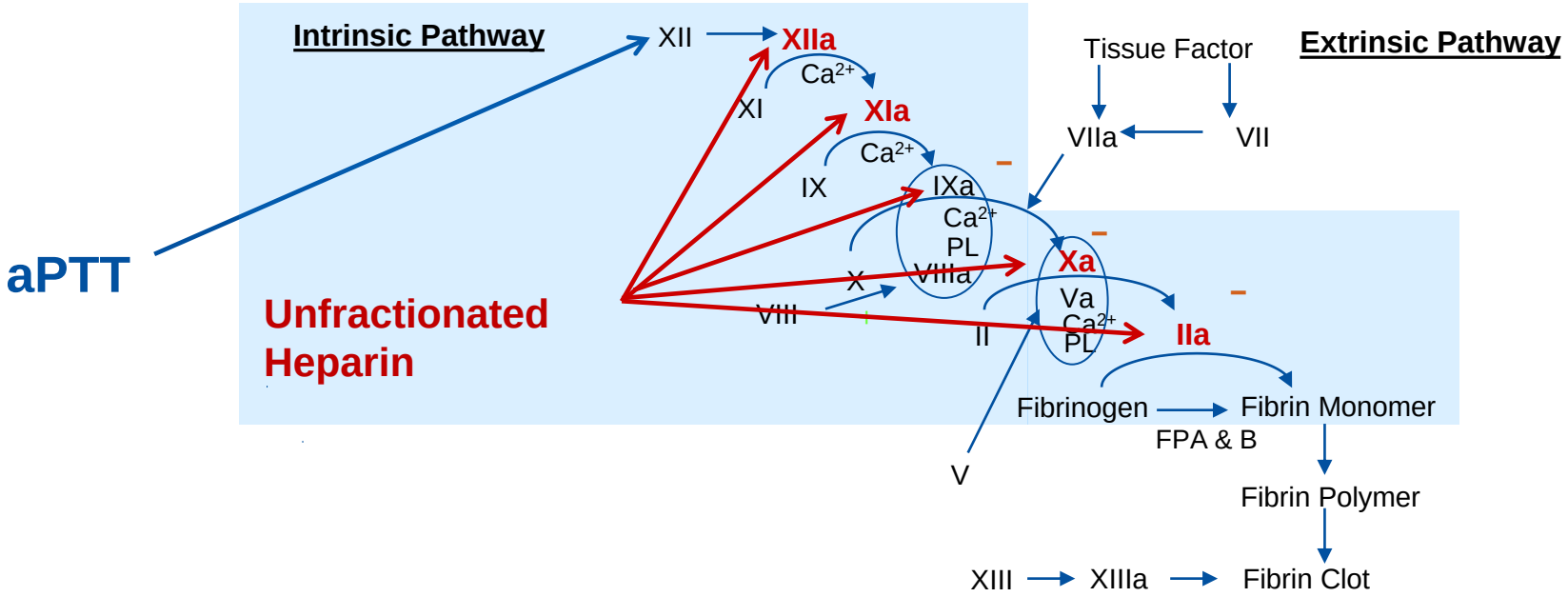
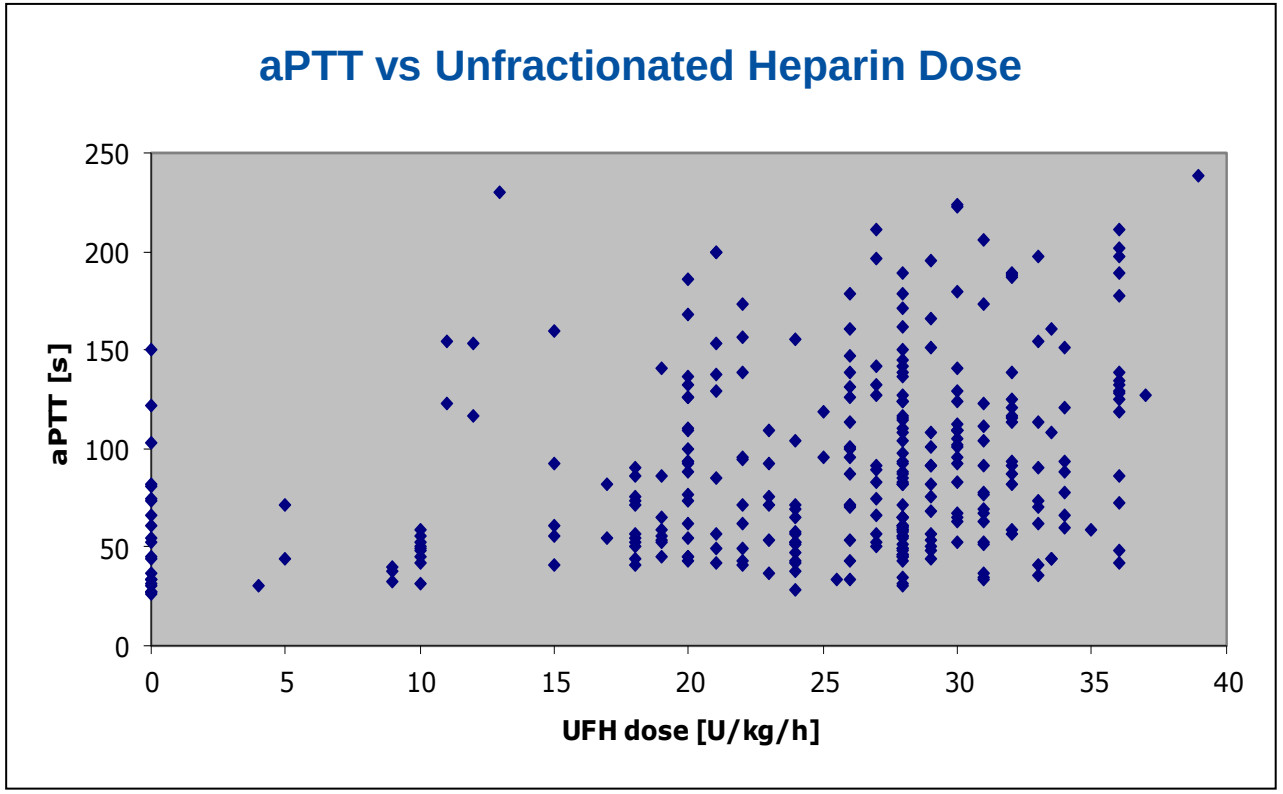


Figure prepared by L. Mitchell

aPTT, activated partial thromboplastin time; FPA, fibrinopeptide A; FPB, fibrinopeptide B; PL, phospholipid

Young. Hematology Am Soc Hematol Educ Program 2015;2015:111

Unfractionated heparin is challenging to monitor in children due to differences in plasma levels of coagulation factors with age



Would the relationship between a direct thrombin inhibitor and laboratory tests be more consistent over childhood?

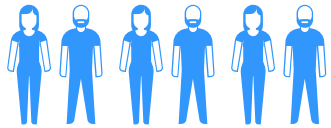
aPTT, activated partial thromboplastin time; UFH, unfractionated heparin

Adapted from Kuhle et al. Haematologica 2007;92:554

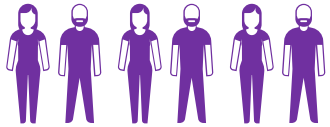
Determining the relationship between dabigatran plasma concentration and coagulation laboratory parameters in pediatric patients with VTE over childhood METHODS

Data from pediatric clinical trials were compared with data from adult clinical trials[1]

Pediatric studies (n=421):
- Three Phase IIa[2–4]
- Two Phase IIb/III[5,6]



Adult studies (n=1881):
- Two Phase III[7,8]



Healthy adult studies (n=97):
- Two Phase I[9,10]

VTE, venous thromboembolism

1. Mitchell et al. Thromb Haemost 2022 *in press*; 2. Halton et al. Thromb Haemost 2017;117:2168; 3. Halton et al. J Thromb Haemost 2017;15:2147; 4. Halton et al. Thromb Haemost 2016;116:461; 5. Halton et al. Lancet Haematol 2021;8:e22; 6. Brandão et al. Blood 2020;135:491; 7. Schulman et al. NEJM 2009;361:2342; 8. Eriksson et al. Thromb Haemost 2011;105:721; 9. Glund et al. Lancet 2015;386:680; 10. Glund et al. Clin Pharmacokinet 2017;56:41

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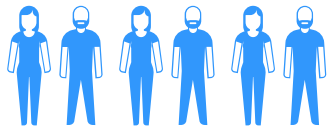

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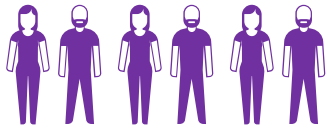

Healthy adult studies (n=97):
- Two Phase I[9,10]

The relationship between dabigatran plasma concentrations and responses to three clinical laboratory assays was assessed:[1]

- Activated partial thromboplastin time (aPTT)
- Ecarin clotting time (ECT)
- Diluted thrombin time (dTT)

VTE, venous thromboembolism

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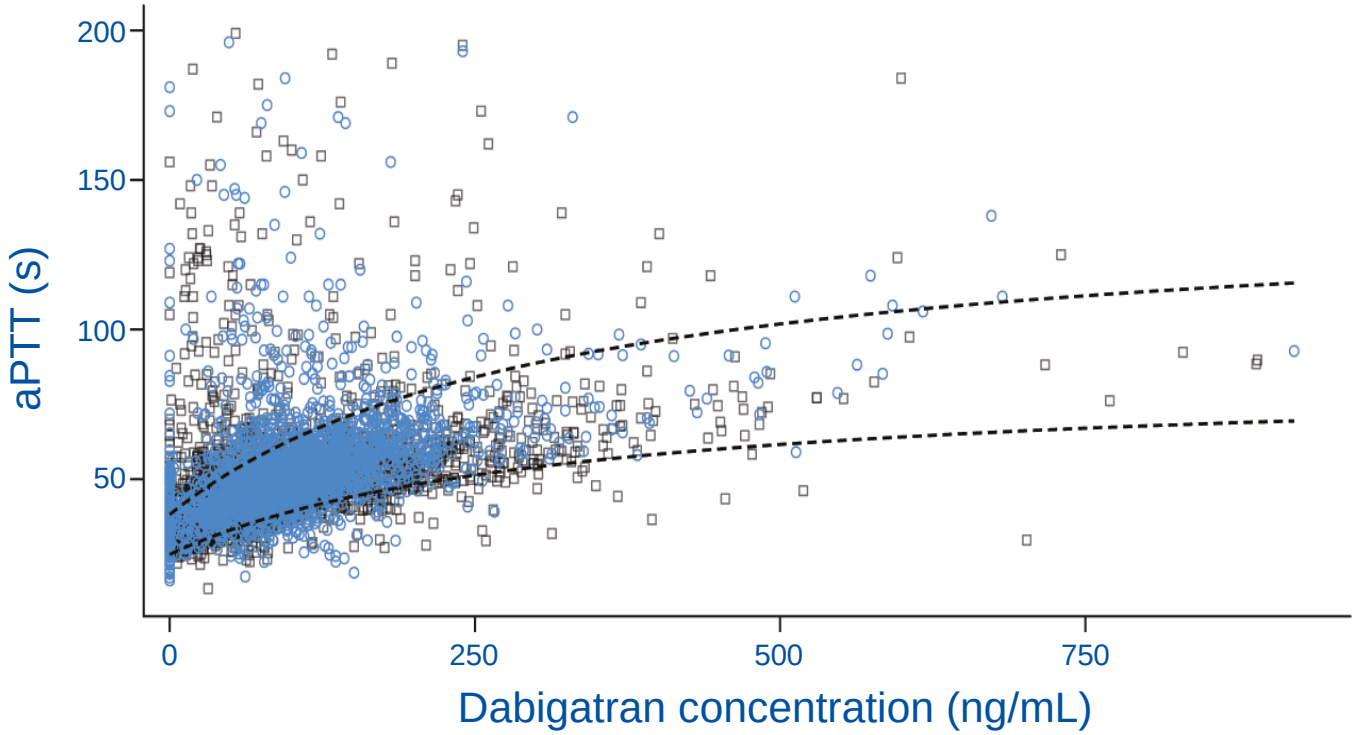
RESULTS: relationship between dabigatran plasma concentrations and aPTT



- - - Model-based 95% prediction interval in healthy adults (1529 observations; 97 adults)

□ Adult patients (4211 observations; 1881 adults)

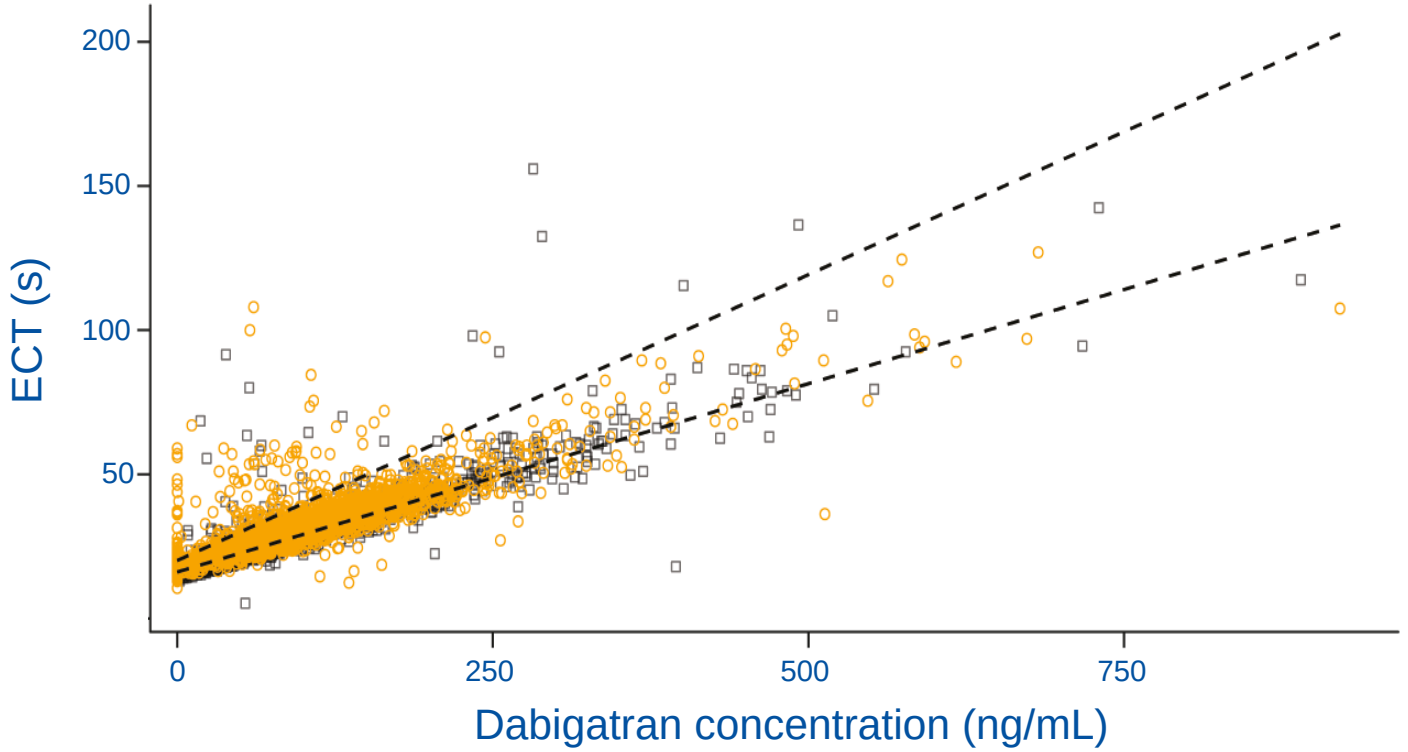
○ Children (2925 observations; 358 children)

Pediatric patients showed a **similar** aPTT response compared with adults; the response was **non-linear**

aPTT, activated partial thromboplastin time

Adapted from Mitchell et al. Thromb Haemost 2022 *in press*

RESULTS: relationship between dabigatran plasma concentrations and ECT



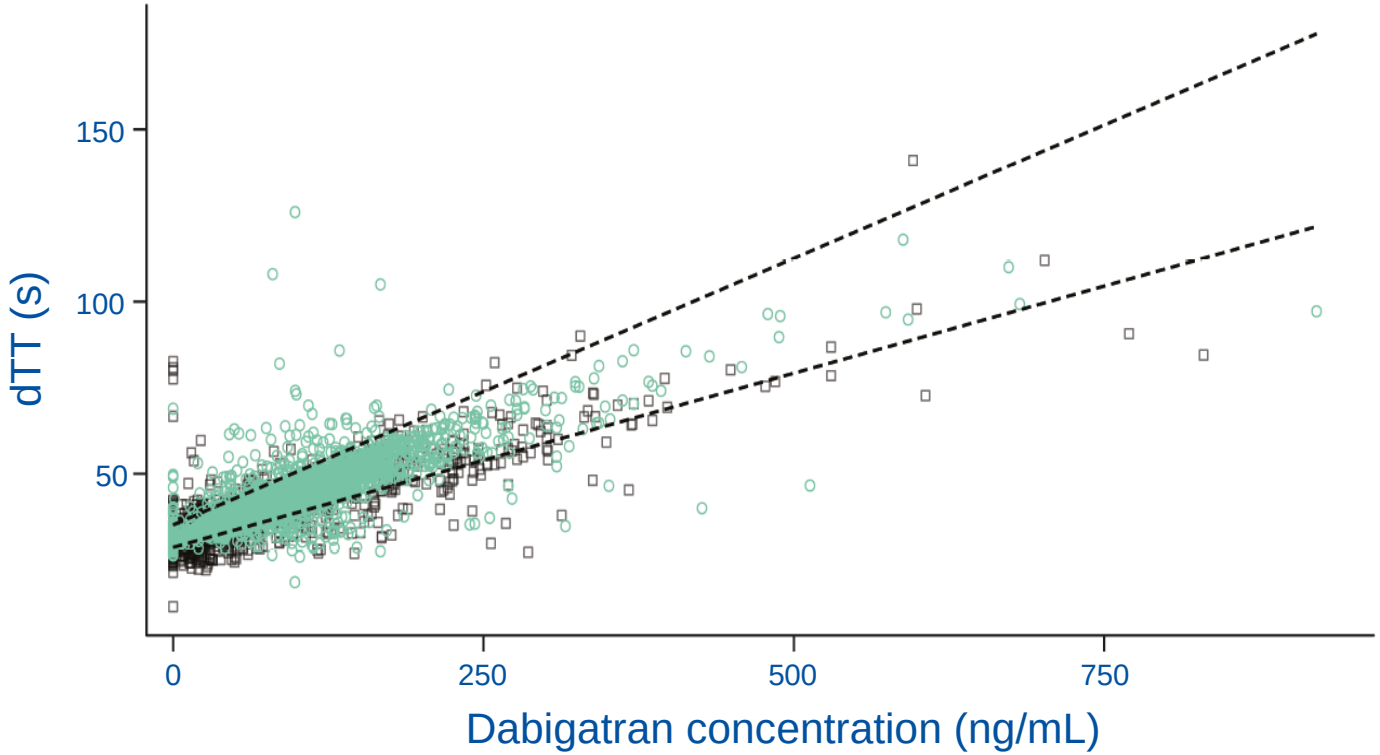
- Model-based 95% prediction interval in healthy adults (1532 observations; 97 adults)
- Adult patients (2285 observations; 1179 adults)
- Children (2929 observations; 357 children)

Pediatric patients showed a **similar** ECT response compared with adults; the response was **linear**

ECT, ecarin clotting time

Adapted from Mitchell et al. Thromb Haemost 2022 *in press*

RESULTS: relationship between dabigatran plasma concentrations and dTT



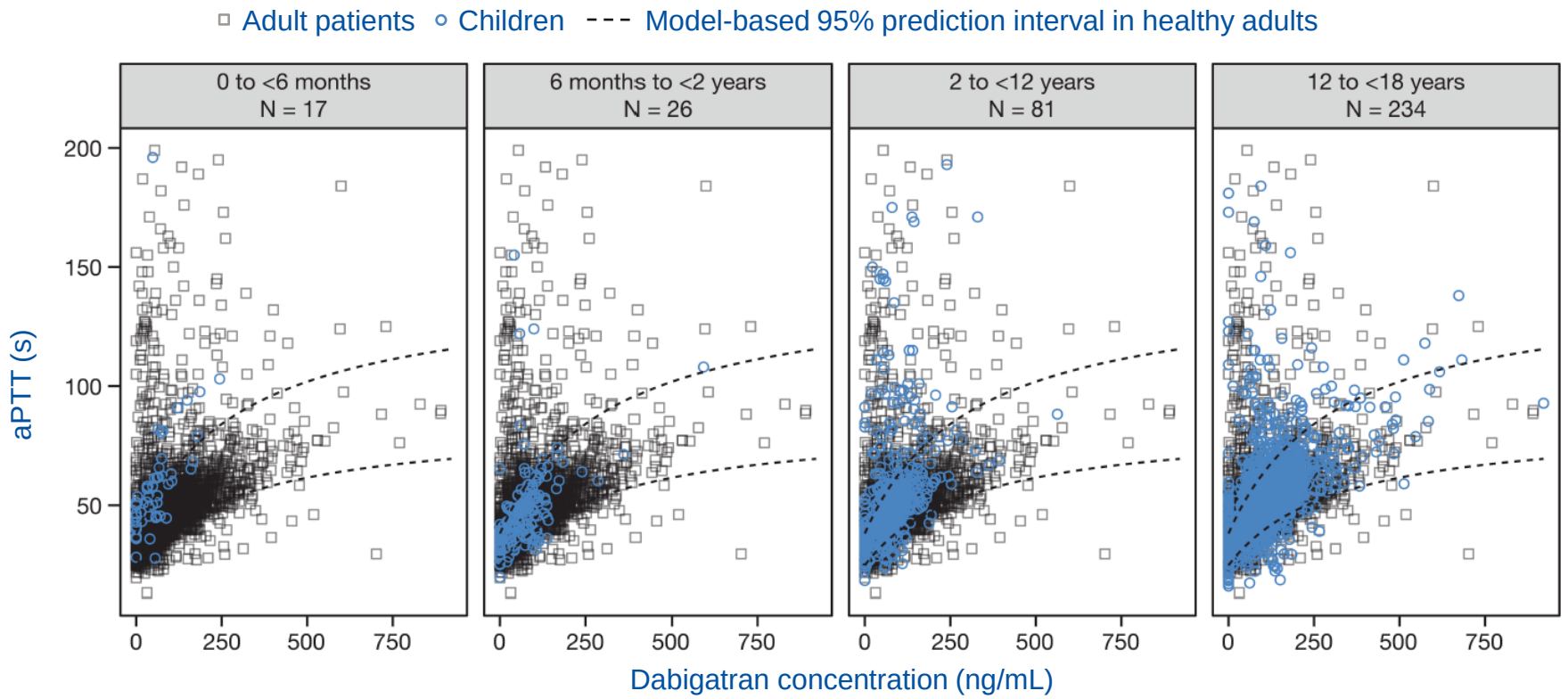
- Model-based 95% prediction interval in healthy adults (1532 observations; 97 adults)
- Adult patients (1940 observations; 1881 adults)
- Children (2348 observations; 324 children)

Pediatric patients showed a **similar** dTT response compared with adults; the response was **linear**

dTT, diluted thrombin time

Adapted from Mitchell et al. Thromb Haemost 2022 *in press*

RESULTS: relationship between dabigatran plasma concentrations and aPTT over childhood

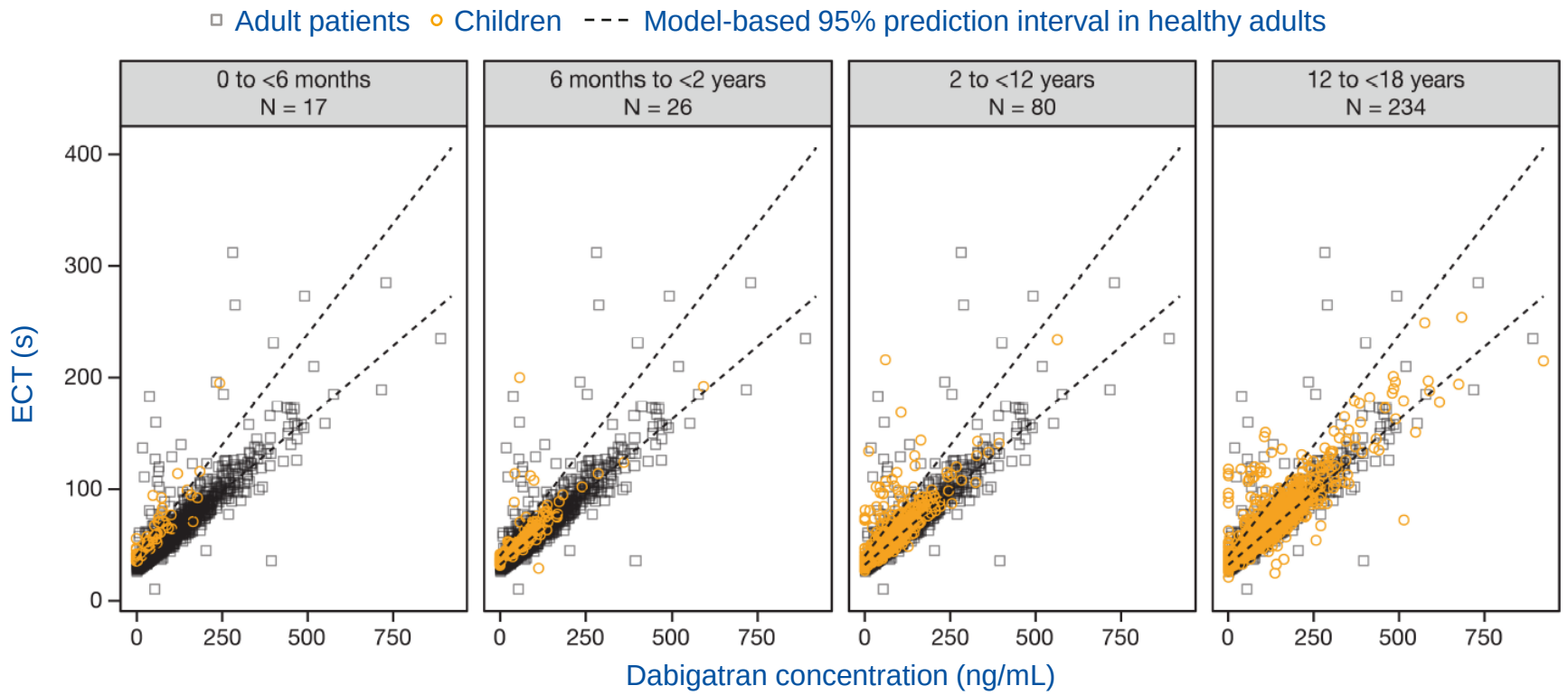


aPTT was slightly increased in younger children; results in older children were comparable to those in adults

aPTT, activated partial thromboplastin time

Adapted from Mitchell et al. Thromb Haemost 2022 *in press*

RESULTS: relationship between dabigatran plasma concentrations and ECT over childhood



ECT was slightly increased in younger children; results in older children were comparable to those in adults

ECT, ecarin clotting time

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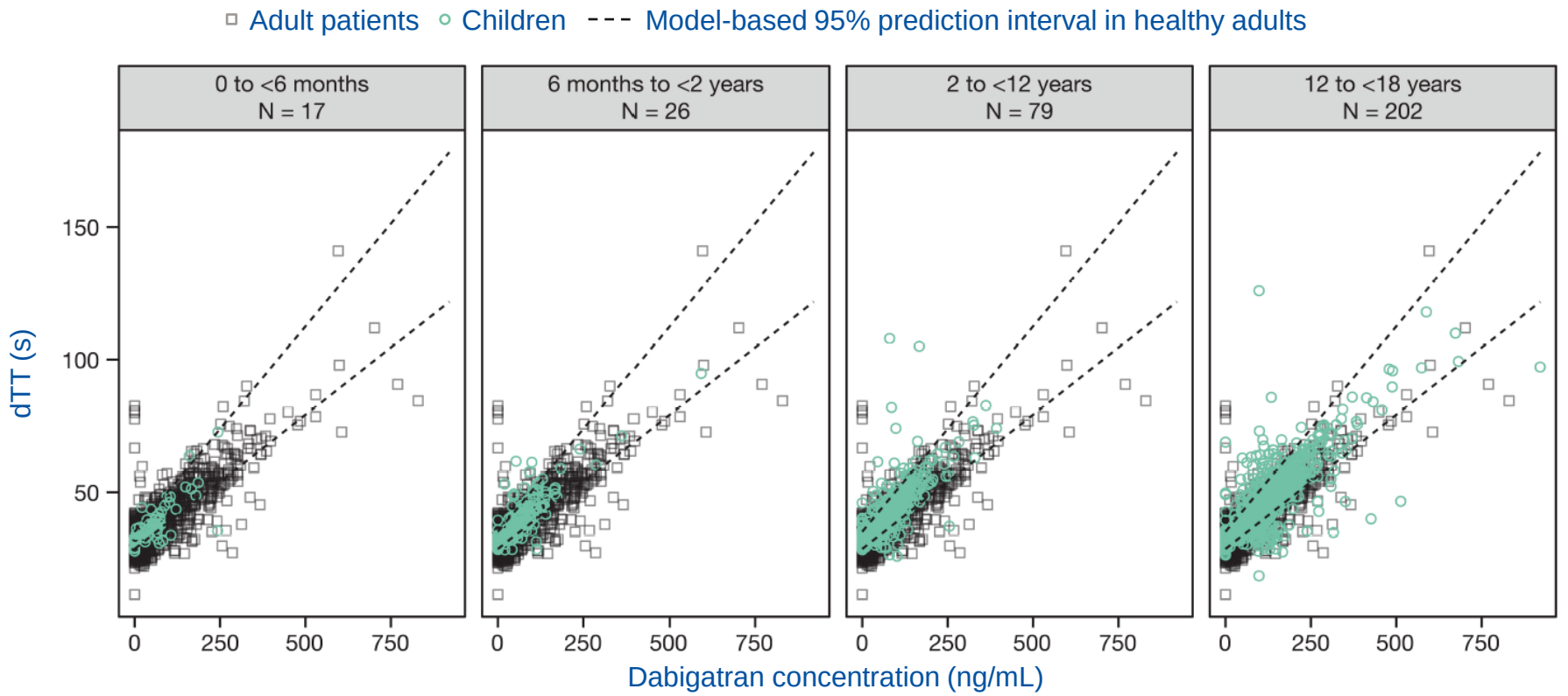

No age-related differences were observed for dTT

dTT, diluted thrombin time

Adapted from Mitchell et al. Thromb Haemost 2022 *in press*

RESULTS: assay baseline results over childhood from the five pediatric studies included in this analysis

		0–6 months	6 months to <2 yrs	2 to <12 yrs	12 to <18 yrs
aPTT	**Baseline, s**	**41 (28–51)**	**35 (20–65)**	**35 (18–91)**	**34 (16–313)**
	Patients, n	11	26	74	210
ECT	**Baseline, s**	**40 (36–56)**	**36 (32–42)**	**34 (27–75)**	**35 (21–118)**
	Patients, n	11	26	72	210
dTT	**Baseline, s**	**32 (28–33)**	**32 (28–40)**	**32 (28–46)**	**32 (26–69)**
	Patients, n	10	25	61	125

Despite changes in the hemostatic system over childhood, there were only minor age-related differences in the aPTT and ECT assay responses, whereas dTT was unaffected by age

Baseline seconds shown as median (range). aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time

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Summary

- Developmental hemostasis in children affects the relationship of coagulation assays to varying plasma levels of classical anticoagulants[1–4]
- Compared with adults, pediatric patients showed a similar response of aPTT, ECT, and dTT assays to dabigatran concentrations[5]
- Despite changes in the hemostatic system over childhood, there were only minor age-related differences in the aPTT and ECT assay responses to dabigatran, whereas dTT was unaffected by age[5]

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

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