Pharmacokinetics and Dose Optimization of Anticoagulants in Children with Obesity

A Focus on Enoxaparin

09 November 2022

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- I am an employee and stockholder of Pfizer.
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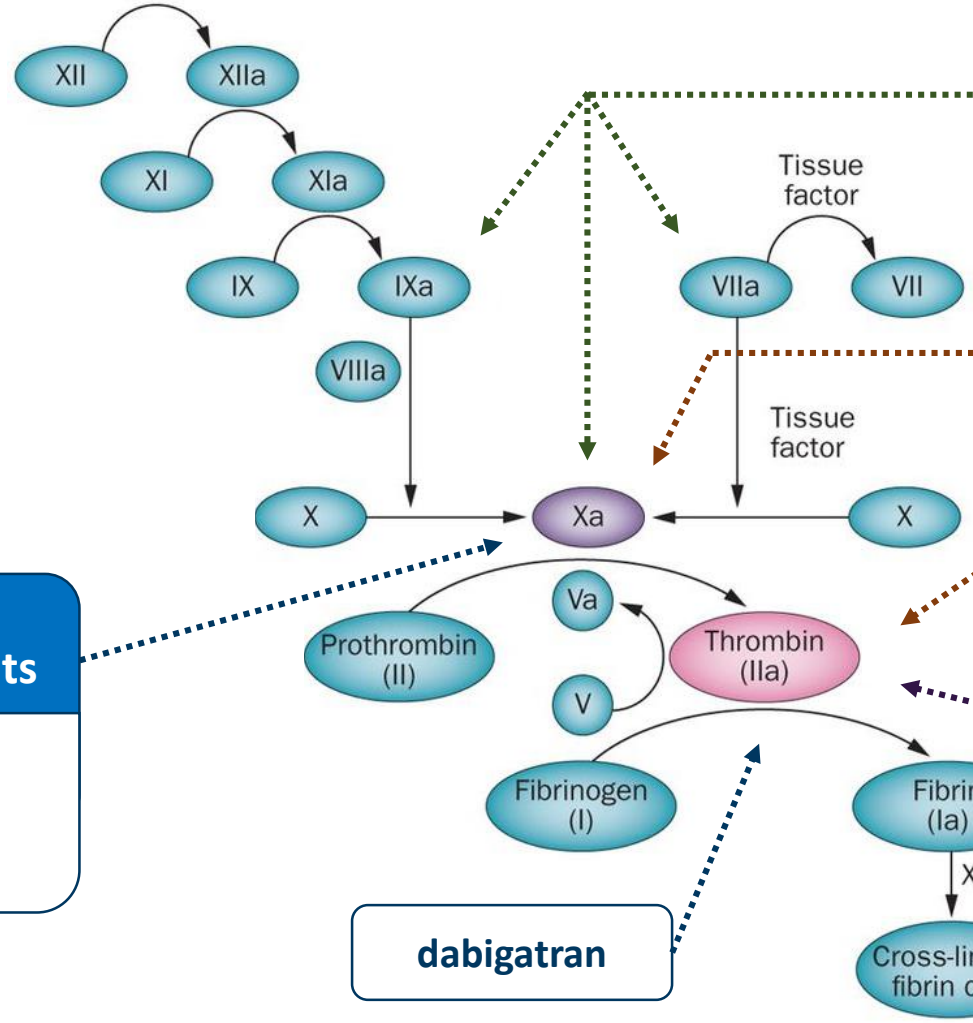
Objectives

- Understand why **precise anticoagulant dosing** is important
- Hypothesize how anticoagulant dosing **may differ in patients with obesity**
- Review **current literature** of anticoagulant dosing in **children with obesity**
- Focus on enoxaparin:
  - How to use **real world data and modeling and simulation** to better understand **enoxaparin in children with obesity**

Anticoagulants are a broad and varied drug class



Vitamin K Reductase Inhibitors

warfarin

Heparins

unfractionated heparin
enoxaparin
dalteparin
fondaparinux

Direct-Acting Oral Anticoagulants

apixaban
edoxaban
rivaroxaban

dabigatran

Direct Thrombin Inhibitors

argatroban
bivalirudin

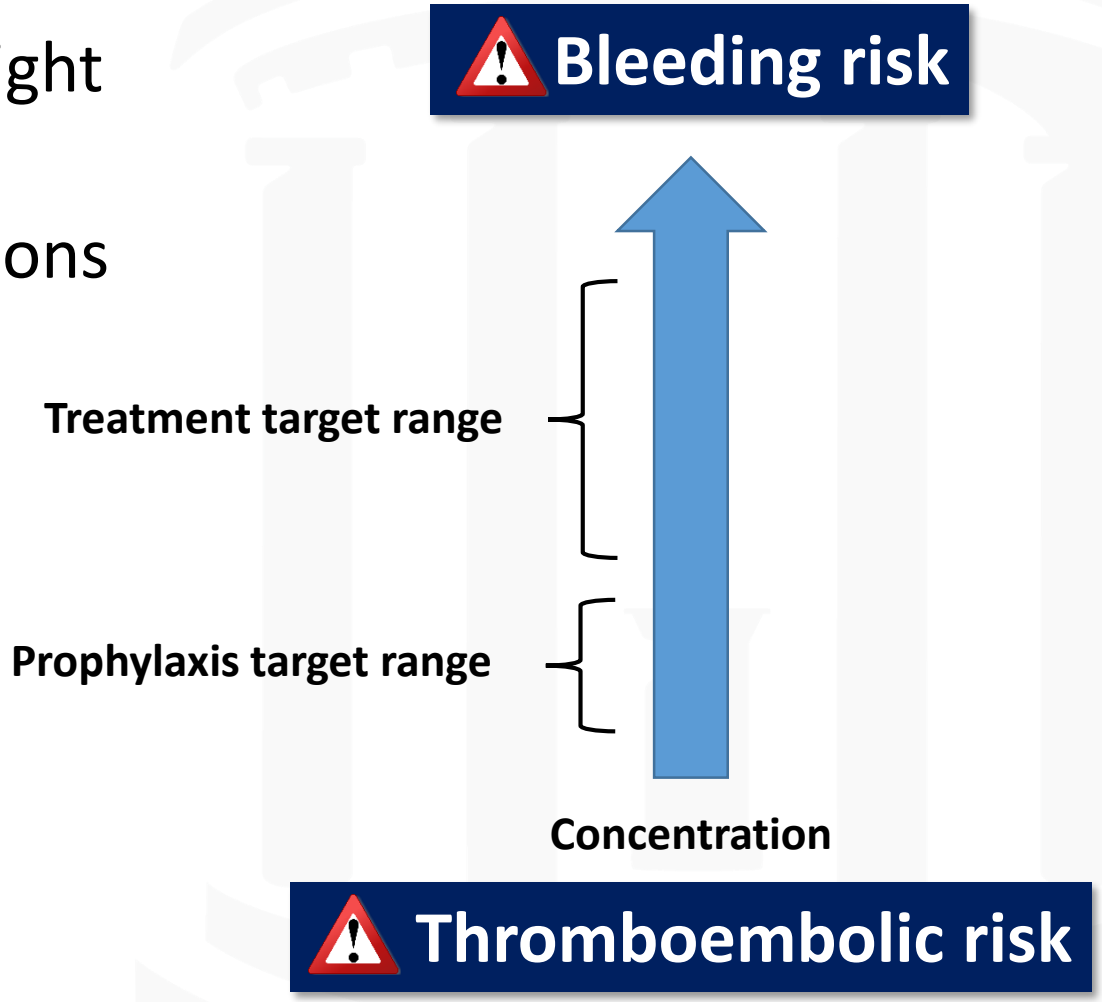
Sabir et al. Nat Rev Cardiol. 2014.

Anticoagulants have narrow therapeutic indices, often requiring dose monitoring

- Many are dosed based on body weight
- Dose monitoring in special populations

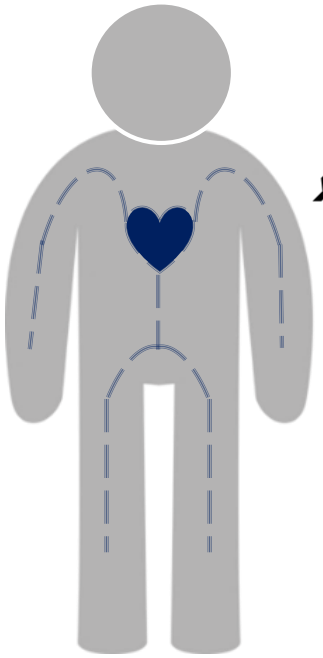
Surrogate Measurements

INR
aPTT
ACT
anti-Xa



ACT: activated clotting time
INR: international normalized ratio
PTT: partial thromboplastin time

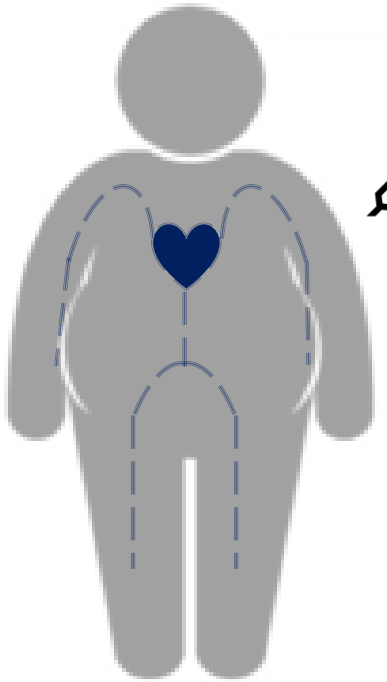
Patients with obesity may be at risk of supra-therapeutic anticoagulant exposure



1 mg/kg

70 kg patient: 70 mg dose

WITHOUT OBESITY



1 mg/kg

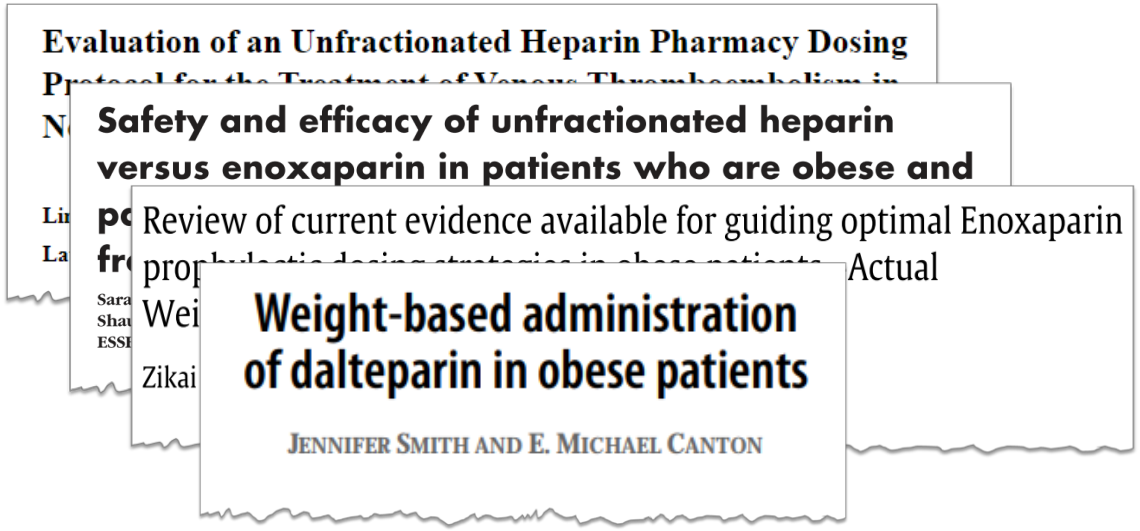
150 kg patient: 150 mg dose

WITH OBESITY

$$\uparrow Concentration = \frac{Dose}{Volume} \uparrow$$

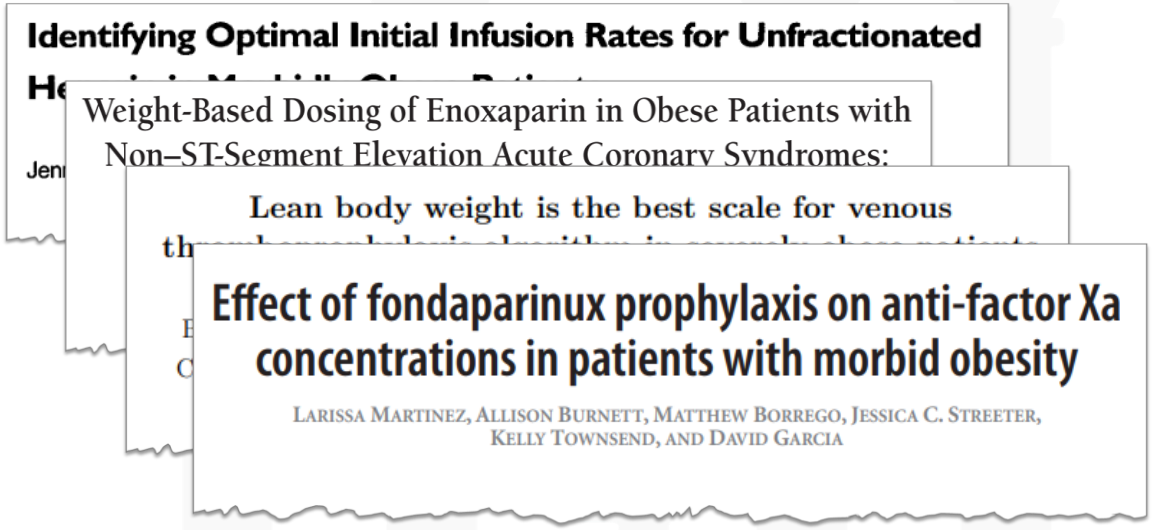
Appropriate heparin dosing in adults with obesity is still debated

Studies supporting recommended dosing[1-4]:



- A minority of adults with obesity received reduced dosing
- No significant difference in peak concentration
- No difference in bleeding events

Studies supporting reduced dosing[5-8]:



- Many real world patients with obesity received reduced dosing
- Reduced dosing better achieved concentration in the target range
- Reduced dosing with obesity reduced bleeding events

See slide 31 for list of references.

Appropriate anticoagulant dosing in children with obesity is unclear

Vitamin K Reductase Inhibitors	
warfarin	↓ Dosing with obesity[1-2]

Heparins	
unfractionated heparin	↓ Dosing with obesity[3-4] No adjustment for obesity[5]
enoxaparin	↓ Dosing with obesity[6] No adjustment for obesity[7]
dalteparin	No adjustment for obesity[8]
fondaparinux	*No published data*

Direct Thrombin Inhibitors	
argatroban bivalirudin	*No published data*

Direct-Acting Oral Anticoagulants	
apixaban edoxaban rivaroxaban dabigatran	*No published data*

- **Understanding pediatric anticoagulant dosing requires characterizing age, obesity status, and their interplay.**

See slide 32 for list of references.

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See slide 32 for list of references.

Children with obesity may have altered warfarin exposure

Methods: Retrospective chart review children 1-12 years old (n = 184)

Category	Odds for elevated INR value	P-value
Obesity	0.24 (0.06-0.86)	< 0.05

Odds ratio (95% confidence interval)

Methods: Retrospective chart review of children 2-18 years old

Characteristic	With Obesity (n = 10)	Without Obesity (n = 20)	P-value
Initial warfarin dose (mg/kg)	0.06 ± 0.02	0.11 ± 0.04	< 0.01
Maximum warfarin dose (mg/kg)	0.09 ± 0.04	0.13 ± 0.05	0.04
Supratherapeutic INR value	1 (10%)	14 (70%)	0.09
Time to therapeutic INR (days)	6 (4-28)	3 (1-10)	< 0.01

Values presented as mean ± standard deviation, n (%), or median (range).

INR: international normalized ratio

Moffett et al. Pediatr Blood Cancer. 2012.
Moffett et al. J Pediatr Hematol Oncol. 2014.

Appropriate anticoagulant dosing in children with obesity is unclear

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Children with obesity receiving heparin exhibit supratherapeutic anti-Xa levels

Methods: Retrospective BMI-based sub-analysis of children 2-19 years old

Characteristic	With Obesity (n = 22)	Without Obesity (n = 34)	P-value
Time to therapeutic anti-Xa (h)	4 (2-17)	12 (4-96)	0.02
First anti-Xa (IU/mL)	0.61 (0.09-2.23)	0.24 (0.09-1.02)	0.01
Supratherapeutic first anti-Xa level	10 (45.5%)	3 (8.8%)	< 0.01
Any supratherapeutic anti-Xa level	17 (77.3%)	12 (35.3%)	< 0.01
Major bleed	1 (4.5%)	1 (2.9%)	0.99
Initial aPTT	101 (40-250)	67 (34-250)	0.07
Supratherapeutic first aPTT	11 (57.9%)	6 (18.8%)	< 0.01
Any supratherapeutic aPTT	16 (84.2%)	21 (65.6%)	0.15

Note: Data are presented as n (%) or median (range). P-values result from chi-square, Fisher's exact, or Wilcoxon rank sum test.

aPTT: activated partial thromboplastin time
BMI: body mass index
IU: international units

Kuhn et al. Pediatr Blood Cancer. 2021.

Appropriate anticoagulant dosing in children with obesity is unclear

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Appropriate enoxaparin dosing in children with obesity is unclear

Reduced dosing of enoxaparin for venous thromboembolism in overweight and obese adolescents: a single institution retrospective review

Stephanie Hoffman MD[1] | Chi Braunreiter MD[2,3]

- 12-18 year-olds (n = 30) with obesity and overweight
- Compared reduced (< 0.9 mg/kg) versus recommended dosing
- Both regimens achieved equivalent concentrations
- No adverse outcomes

Comparison of Anti-Xa Levels in Obese and Non-Obese Pediatric Patients Receiving Treatment Doses of Enoxaparin

Ashley A. Richard, PharmD[1], Shelly Kim, PharmD[1], Brady S. Moffett, PharmD, MPH[1], Lisa Bomgaars, MD[2], Donald Mahoney, Jr., MD[2], and Donald L. Yee, MD[2]

- 2-18 year-olds (n = 60) with and without obesity
- Mean therapeutic dose was 26% lower with obesity
- Concentrations were 21% higher with obesity
- Minimal bleeding for either group

Hoffman et al. *Res. Pract Thromb Haemost.* 2017.
Richard et al. *J Ped.* 2013.

Appropriate enoxaparin dosing in children with obesity is unclear

Use of Real-World Data and Physiologically-Based Pharmacokinetic Modeling to Characterize Enoxaparin Disposition in Children With Obesity

Jacqueline G. Gerhart[1], Fernando O. Carreño[1], Matthew Shane Loop[1], Craig R. Lee[1], Andrea N. Edginton[2], Jaydeep Sinha[1,3], Karan R. Kumar[4,5], Carl M. Kirkpatrick[6], Christoph P. Hornik[4,5] and Daniel Gonzalez[1,*] on behalf of the Best Pharmaceuticals for Children Act – Pediatric Trials Network Steering Committee[†]

OBJECTIVE:

Use **real world data** to characterize differences in **enoxaparin** disposition in children with and without **obesity**.

Gerhart et al. *Clin Pharmacol Ther.* 2022.

OBJECTIVE: Use real world data to characterize differences in enoxaparin disposition

1

Prepare **real world dataset** for analysis.

- Data cleaning and formatting
- Data quality control checks

2

Use real world data to develop a **PBPK model** to better understand mechanistic drivers of enoxaparin concentration

- Developed in adults
- Scaled to children

3

Use the PBPK model to do **dosing simulations** in order to optimize dosing in children with obesity.

- Evaluate recommended dosing
- Explore body size metrics

✓ Extensive dataset of real world patients

✓ Mechanistic characterization of exposure differences

PBPK: physiologically-based pharmacokinetic

Gerhart et al. *Clin Pharmacol Ther.* 2022.

Observed concentrations came from pediatric electronic health record data

Inclusion criteria

- Children 2 – 17 years old
- Receiving enoxaparin for treatment or prophylaxis

Exclusion criteria

- Renal dysfunction (eGFR < 30 mL/min or 90 mL/min/1.73m^2 or CrCl < 75 mL/min/1.73m^2)
- Serum creatinine > 4 mg/dL
- Elevated bilirubin levels (≥ 6 mg/dL)
- On hemodialysis, ECMO, VAD, or dialysis
- Pregnancy
- Neoplasms
- No height or anti-Xa concentration reported

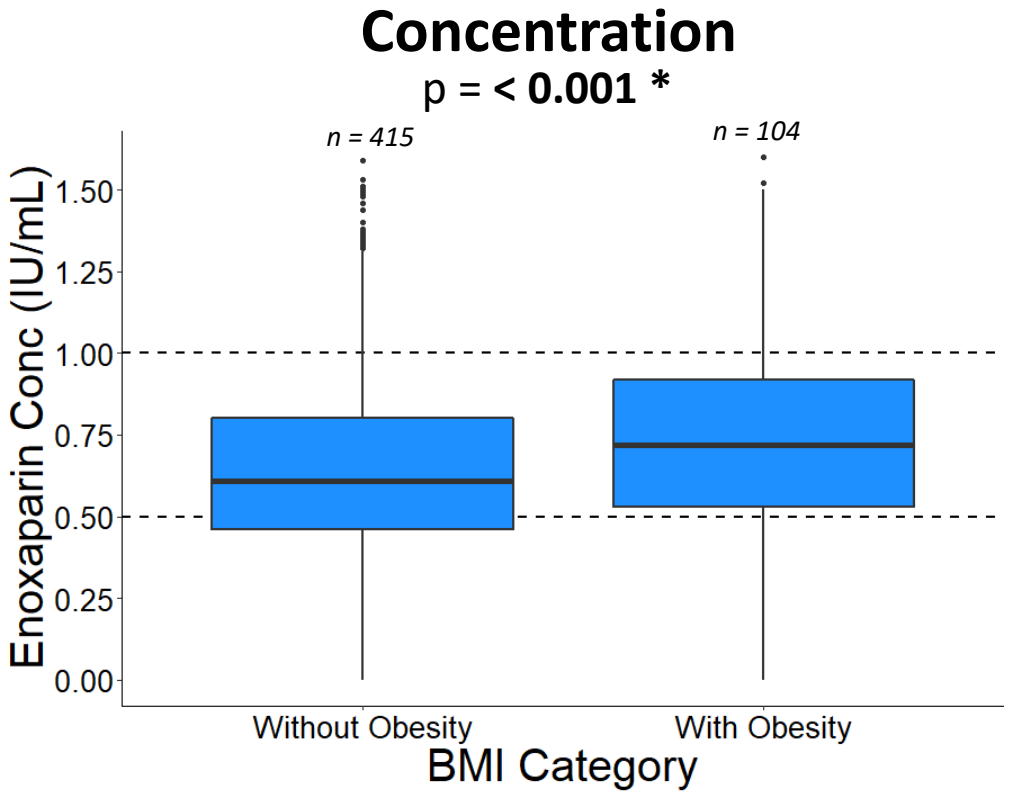
Data	N
Sites	9
Subjects	596
Hospitalizations	1,098
Anti-Xa Samples	2,825

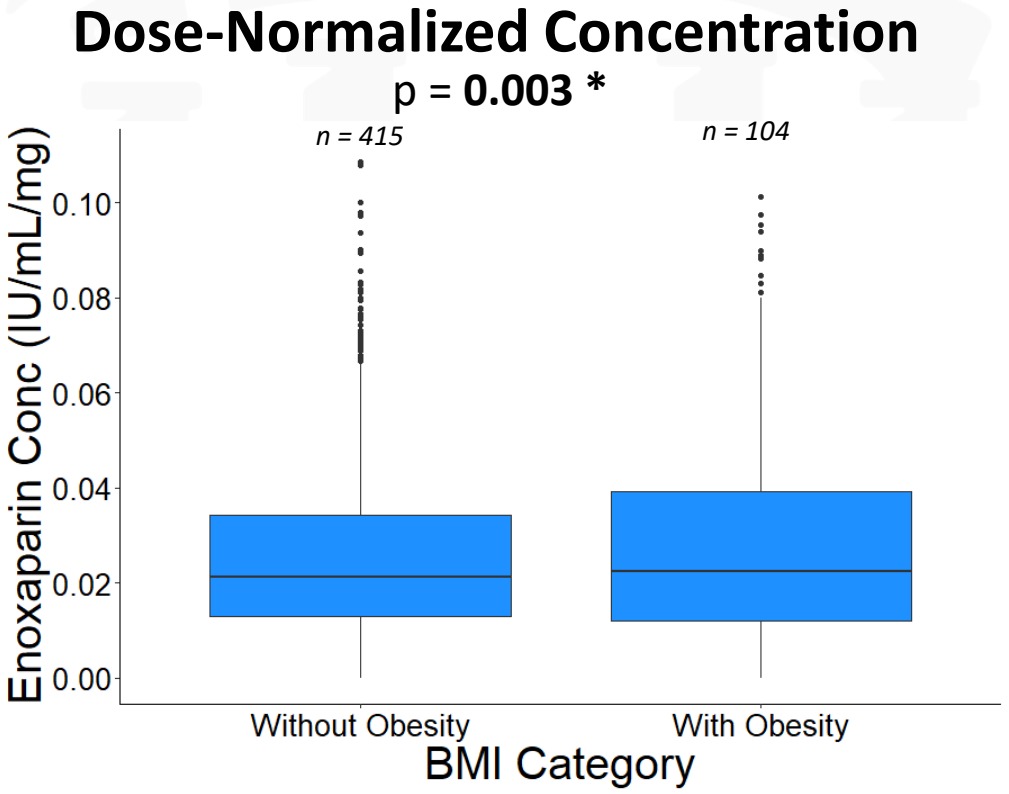
1 Real world dataset → 2 Model development → 3 Dosing simulations

CrCl: creatinine clearance
ECMO: extracorporeal membrane oxygenation
eGFR: estimated glomerular filtration rate
VAD: ventricular assist device

Gerhart et al. *Clin Pharmacol Ther.* 2022.
https://pediatrictrials.org/ptn-creates-data-repository-to-aid-in-pediatric-research

Children with and without obesity have significantly higher enoxaparin concentrations





1 Real world dataset | 2 Model development | 3 Dosing simulations

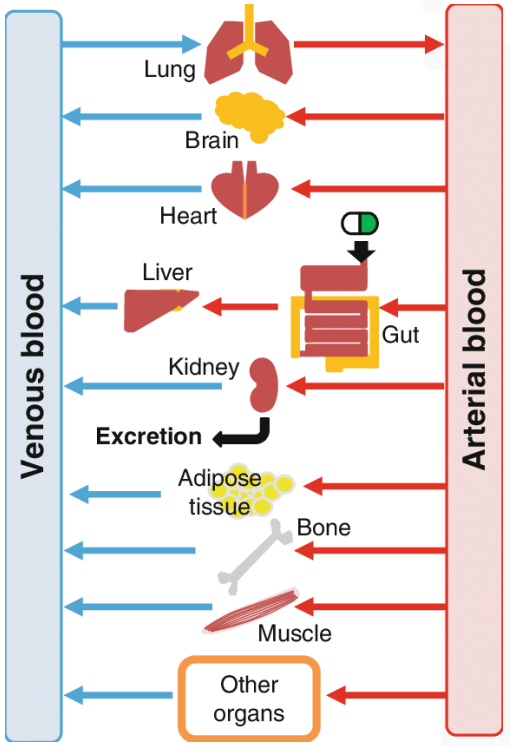
Note: 20 and 18 upper outliers omitted from left and right figures, respectively, for better visualization.

BMI: body mass index
Conc: concentration
IU: international units

Gerhart et al. *Clin Pharmacol Ther.* 2022.

PBPK offers advantages for characterizing drug disposition in children with obesity

Virtual population



Physicochemical properties

System information

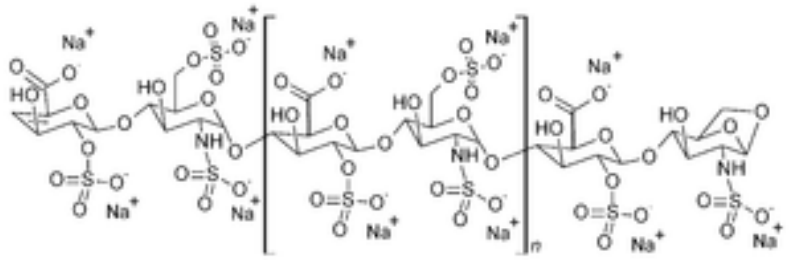
1 Real world dataset | 2 **Model development** | 3 Dosing simulations

PBPK: physiologically-based pharmacokinetic

Barrett et al. *Clin Pharmacol Ther*. 2012.
Gerhart et al. *Front Pharmacol.* 2022.

Key enoxaparin PBPK model parameters

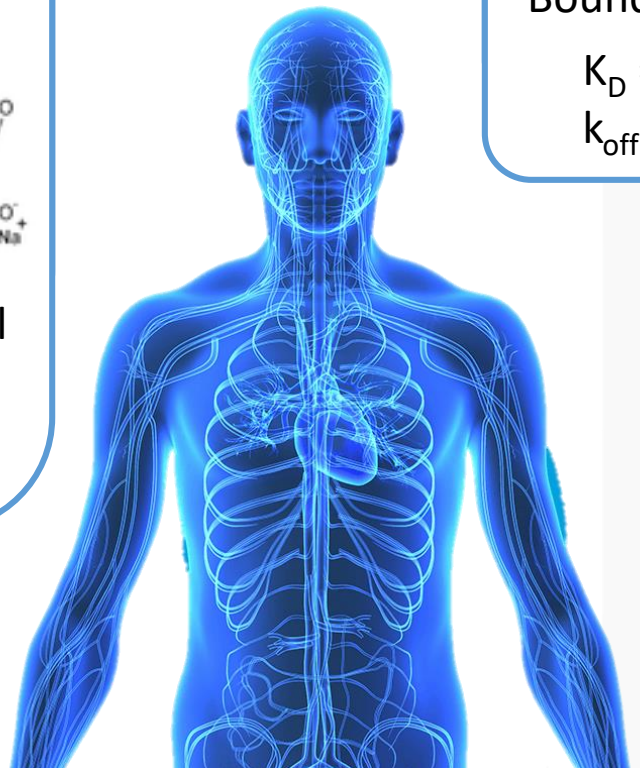
Drug Properties



Average molecular weight: 4500 g/mol
logP: -10.0
1 mg enoxaparin ≈ 100 IU anti-Xa

Absorption

Bioavailability	100%
k_a (1/h)	0.60



Distribution

Bound to ***antithrombin*** in plasma:

K_D = 2.5 µM
k_{off} = 2 1/h

Metabolism

Heparinase:
Intrinsic clearance = 151 mL/min

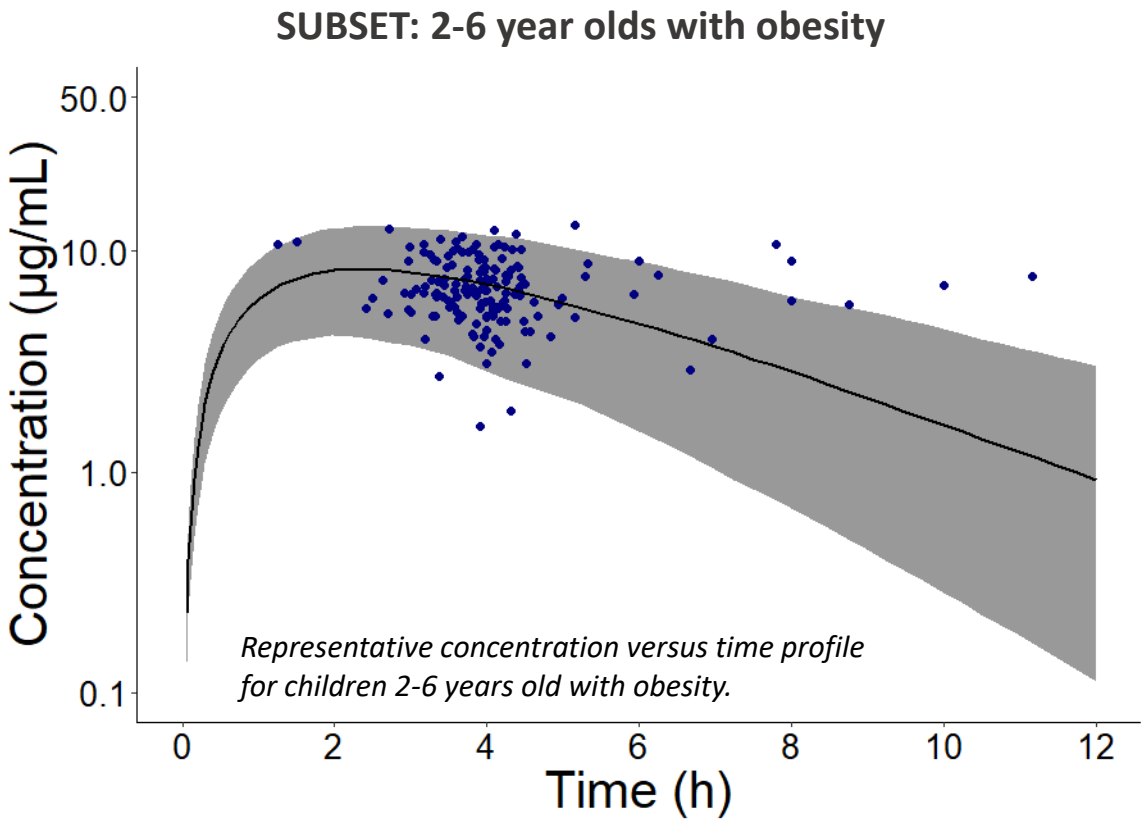
Excretion

Renal clearance:
GFR ($f_{e,urine}$ ≈ 40%)

$f_{e,urine}$: fraction excreted in urine
GFR: glomerular filtration rate
IU: international units
logP: lipophilicity measure
k_a: absorption rate constant
K_D: equilibrium dissociation constant
k_{off}: rate of unbinding
PBPK: physiologically-based pharmacokinetic

Gerhart et al. *Clin Pharmacol Ther.* 2022.
Lovenox FDA label.

PBPK modeling captures observed concentrations from children without and with obesity



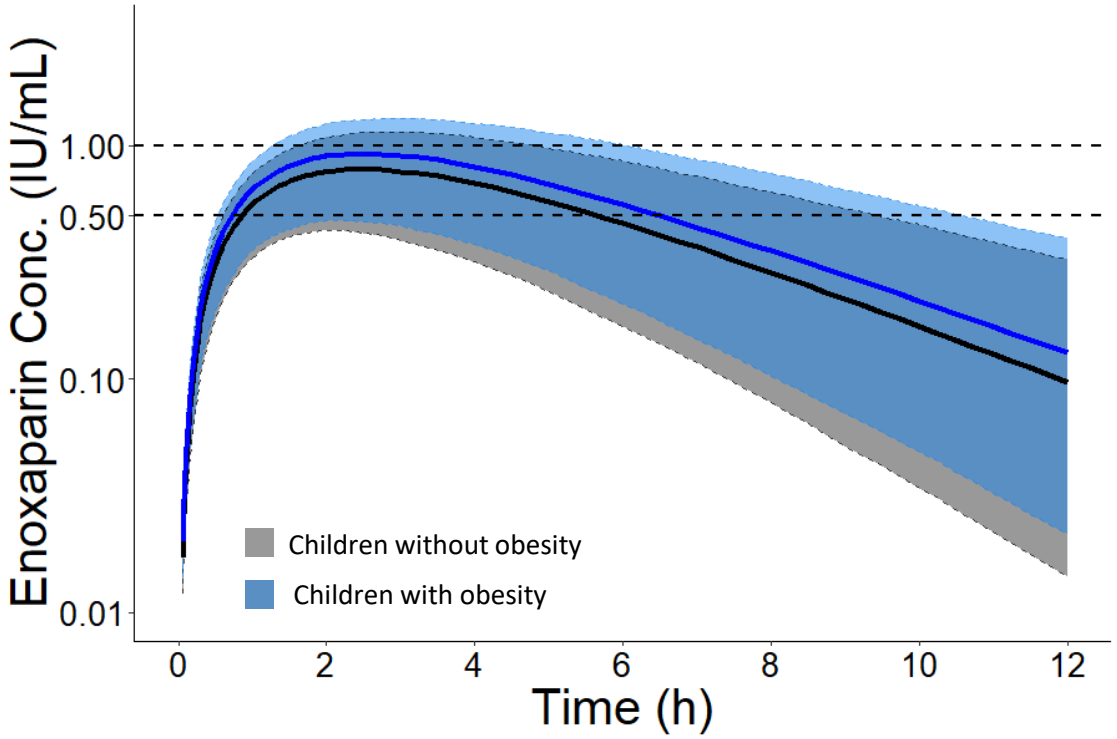
	Children without Obesity	Children with Obesity
AFE	0.87	0.82
Within 90% PI (%)	75.2%	77.2%
Above 90% PI (%)	20.6%	20.5%
Below 90% PI (%)	4.2%	4.1%

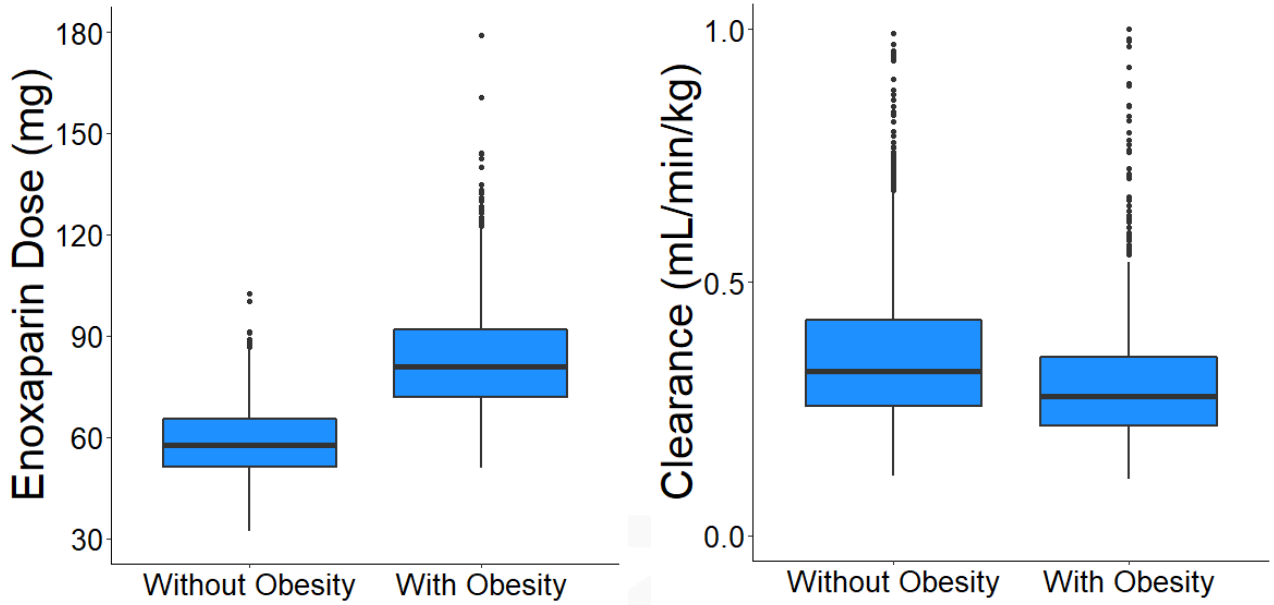
1 Real world dataset | 2 **Model development** | 3 Dosing simulations

AFE: average fold error
PBPK: physiologically-based pharmacokinetic
PI: prediction interval

Gerhart et al. *Clin Pharmacol Ther.* 2022.

PBPK model-estimated changes in enoxaparin disposition with obesity





Above target range:

- **8.9%** children without obesity
- **22.5%** children with obesity

1 Real world dataset
2 Model development
3 **Dosing simulations**

Conc: concentration
IU: international units
PBPK: physiologically-based pharmacokinetic

Gerhart et al. *Clin Pharmacol Ther.* 2022.

Optimizing recommended weight-based enoxaparin dosing

Recommended Dosing

- Treatment: 1 mg/kg BID
- Prophylaxis: 0.5 mg/kg BID

Body Size Metrics

- Total bodyweight (currently recommended)
- Fat-free mass (FFM)

$$FFM\ (males) = \left[0.88 + \left(\frac{0.12}{\left[1 + \left(\frac{age}{13.4}\right)^{-12.7}\right]}\right)\right] * \left[\frac{(9270 * weight)}{6680 + (216 * BMI)}\right]$$

$$FFM\ (females) = \left[1.11 + \left(\frac{-0.11}{\left[1 + \left(\frac{age}{7.1}\right)^{-1.1}\right]}\right)\right] * \left[\frac{(9270 * weight)}{8780 + (244 * BMI)}\right]$$

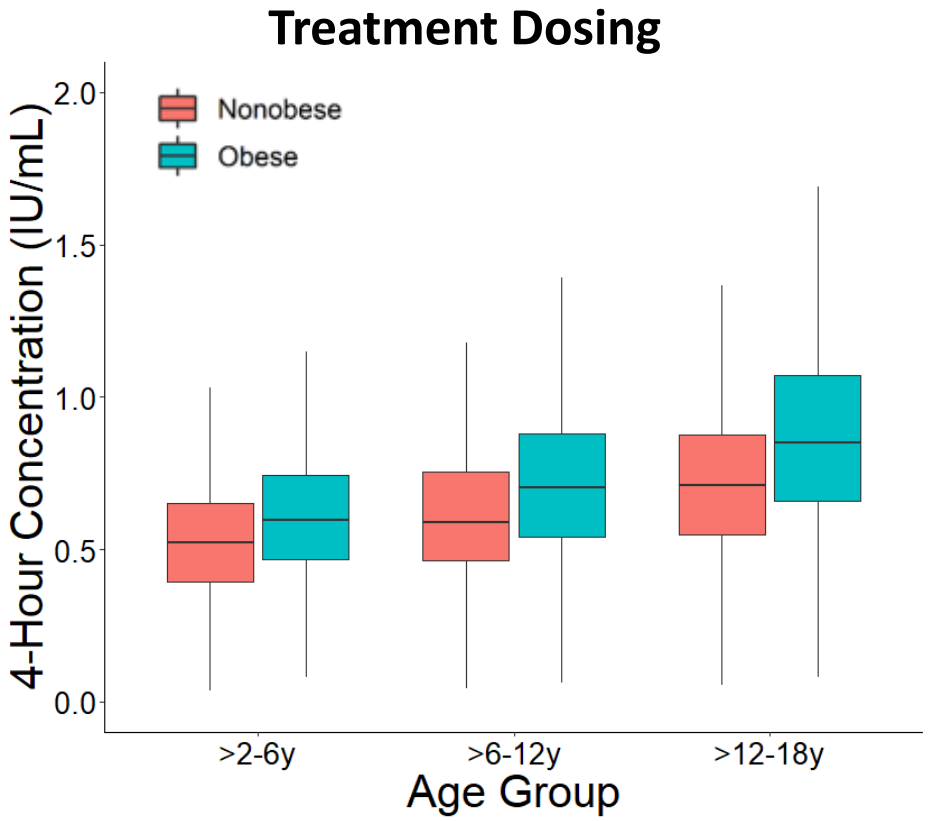
Goal: Match exposure between children with and without obesity.

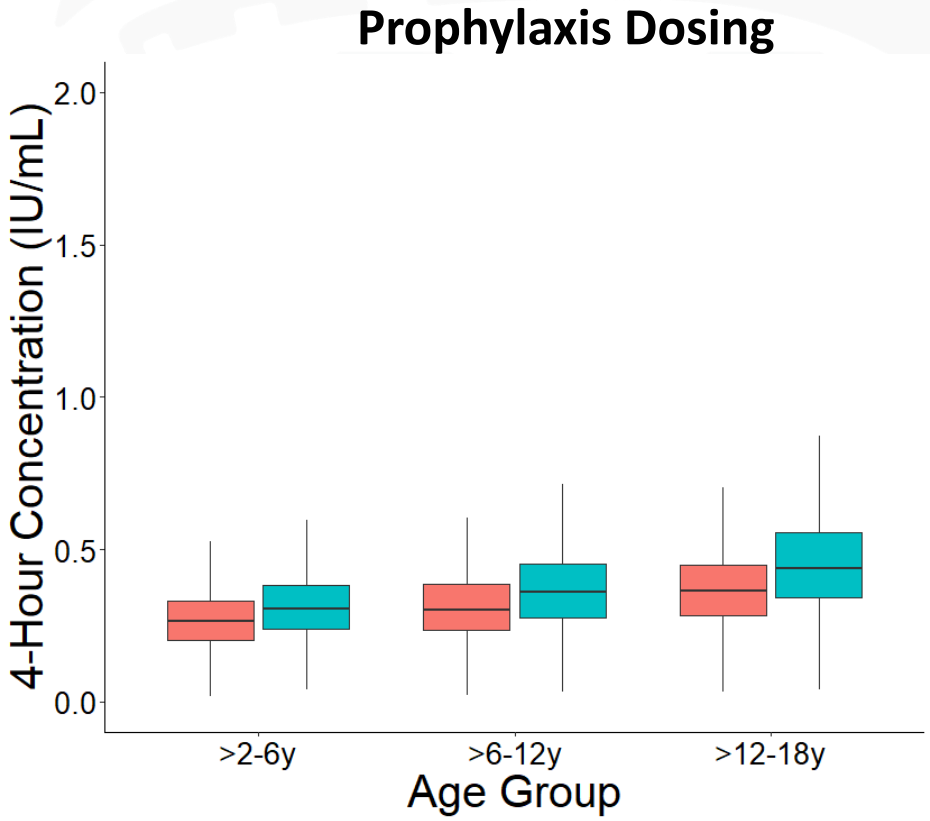
1 Real world dataset | 2 Model development | 3 **Dosing simulations**

BID: twice daily
BMI: body mass index
FFM: fat-free mass

Gerhart et al. *Clin Pharmacol Ther.* 2022.
Al-Sallami et al. *Clin Pharmacokinet.* 2015.

Weight-based dosing results in differences in enoxaparin concentration with obesity and age





1 Real world dataset
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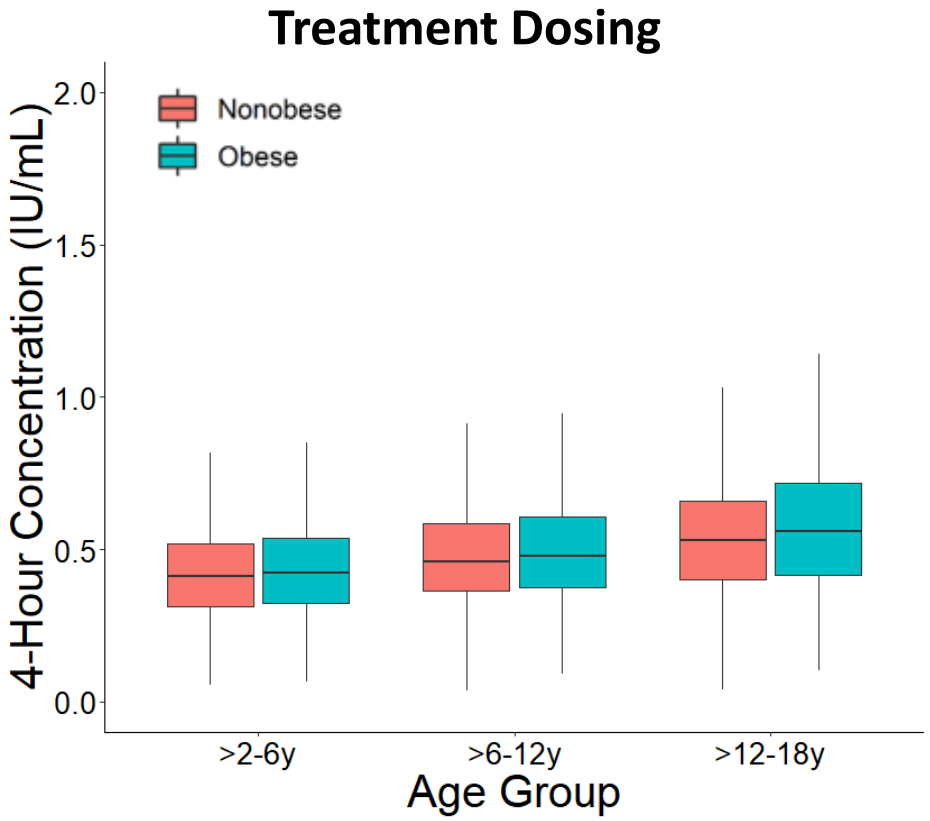
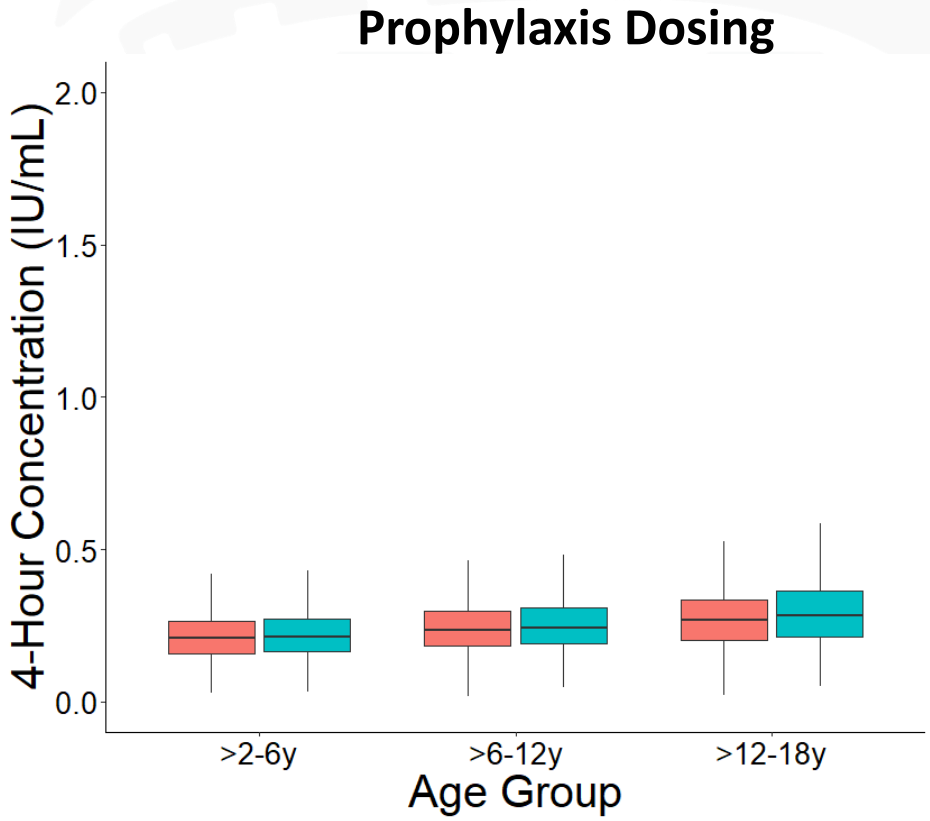
iU: International units

Gerhart et al. *Clin Pharmacol Ther.* 2022.

Fat-free mass dosing equalizes enoxaparin concentration with obesity and age





1 Real world dataset
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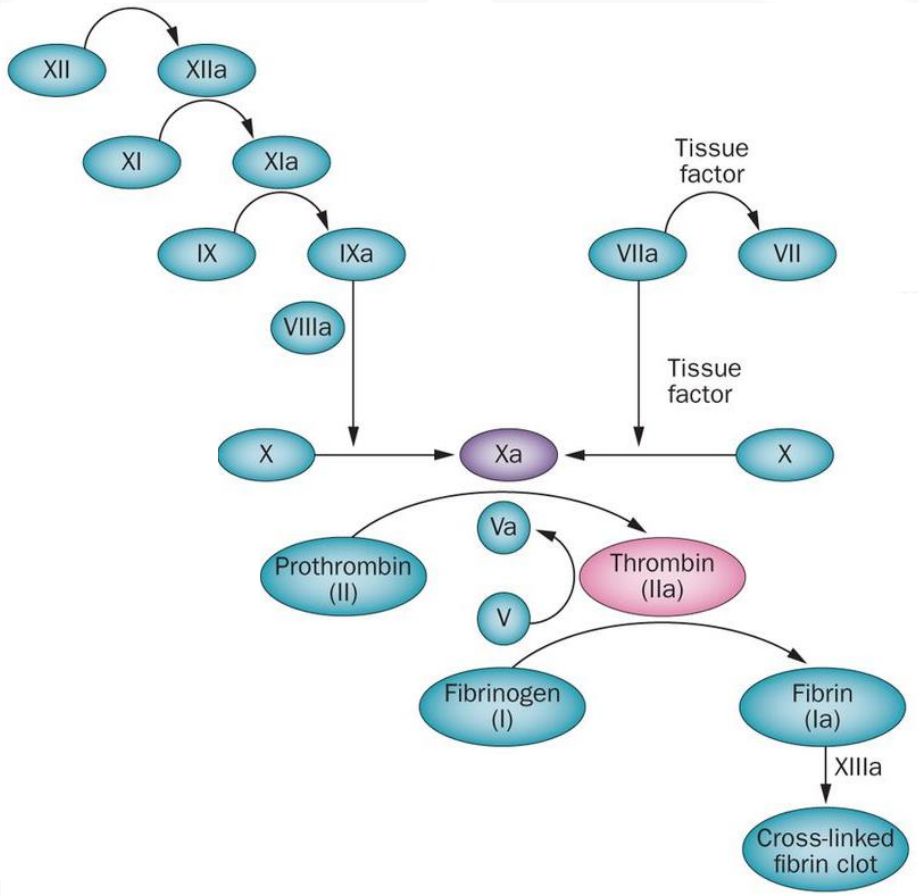
3 **Dosing simulations**

IU: international units

Gerhart et al. *Clin Pharmacol Ther.* 2022.

Future directions: Anticoagulant pharmacodynamics

- **Pediatric** anticoagulant trials
  - Direct thrombin inhibitors, DOACs
- **Dose-response** relationship
  - **Adults versus pediatric** patient populations
- **Obesity-induced** changes in the coagulation cascade



DOACs: direct-acting oral anticoagulants

Sabir et al. Nat Rev Cardiol. 2014.

Conclusions: Results to-date highlight the importance of childhood obesity in anticoagulant dosing

- Most anticoagulant pediatric obesity data published are for **warfarin, heparin, or enoxaparin**.
- Taken together, these studies generally suggest that children with obesity might receive **lower** anticoagulant doses, are **more likely** to have a supratherapeutic concentrations, and **take longer** to achieve therapeutic concentrations relative to children without obesity.
- **Dose monitoring** of anticoagulants can allow for dose adjustments with obesity.
- Children with obesity have statistically significantly **higher** enoxaparin concentrations. **Fat-free mass dosing** leads to **more comparable** 4-hour enoxaparin exposure.
- **Age and obesity status** should be considered in enoxaparin dose selection for children.

Gerhart et al. *Clin Pharmacol Ther.* 2022.

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  - Craig Lee, PharmD, PhD
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Obesity and weight may impact appropriate anticoagulant dosing in adults

Vitamin K Reductase Inhibitors

warfarin	↑ absolute dose with obesity[1-4]

Heparins

unfractionated heparin	↓ weight-based dose with obesity[5-6] Use recommended weight-based dose[7-8]
enoxaparin	↓ weight-based dose with obesity[9-14] Use recommended weight-based dose[15-19]
dalteparin	↓ absolute dose with obesity[20] Use weight-based dose with obesity[21-23] Use ideal weight-based dose with obesity[24]
fondaparinux	↓ weight-based dose with obesity[25]

Direct Thrombin Inhibitors

argatroban	Use recommended weight-based dose[26-27]
bivalirudin	Use recommended weight-based dose[28]

Direct-Acting Oral Anticoagulants

apixaban	Use recommended absolute dose[29-31]
edoxaban	*No published data*
rivaroxaban	Use recommended absolute dose[31-33]
dabigatran	*No published data*

See slides 34-37 for list of references.

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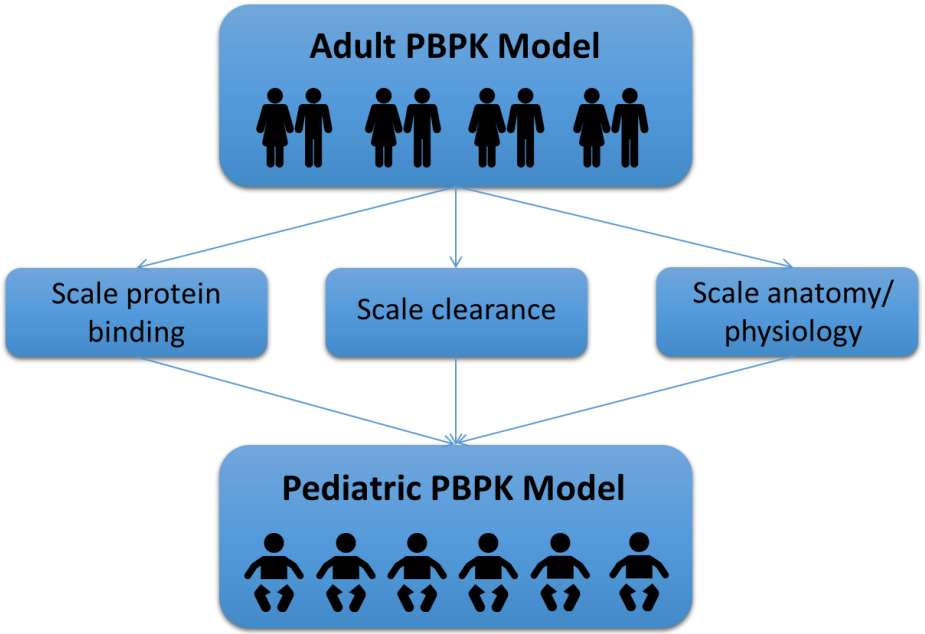
Scaling the adult PBPK to children

Scaling to Children



Expanding to Children with Obesity

Organs

- ↑ Blood flow
- ↑ Weight

Renal Clearance

- ↑ Glomerular filtration rate

Protein Binding

- ↔ Albumin
- ↔ AAG
- ↔ Hematocrit

Hepatic Clearance

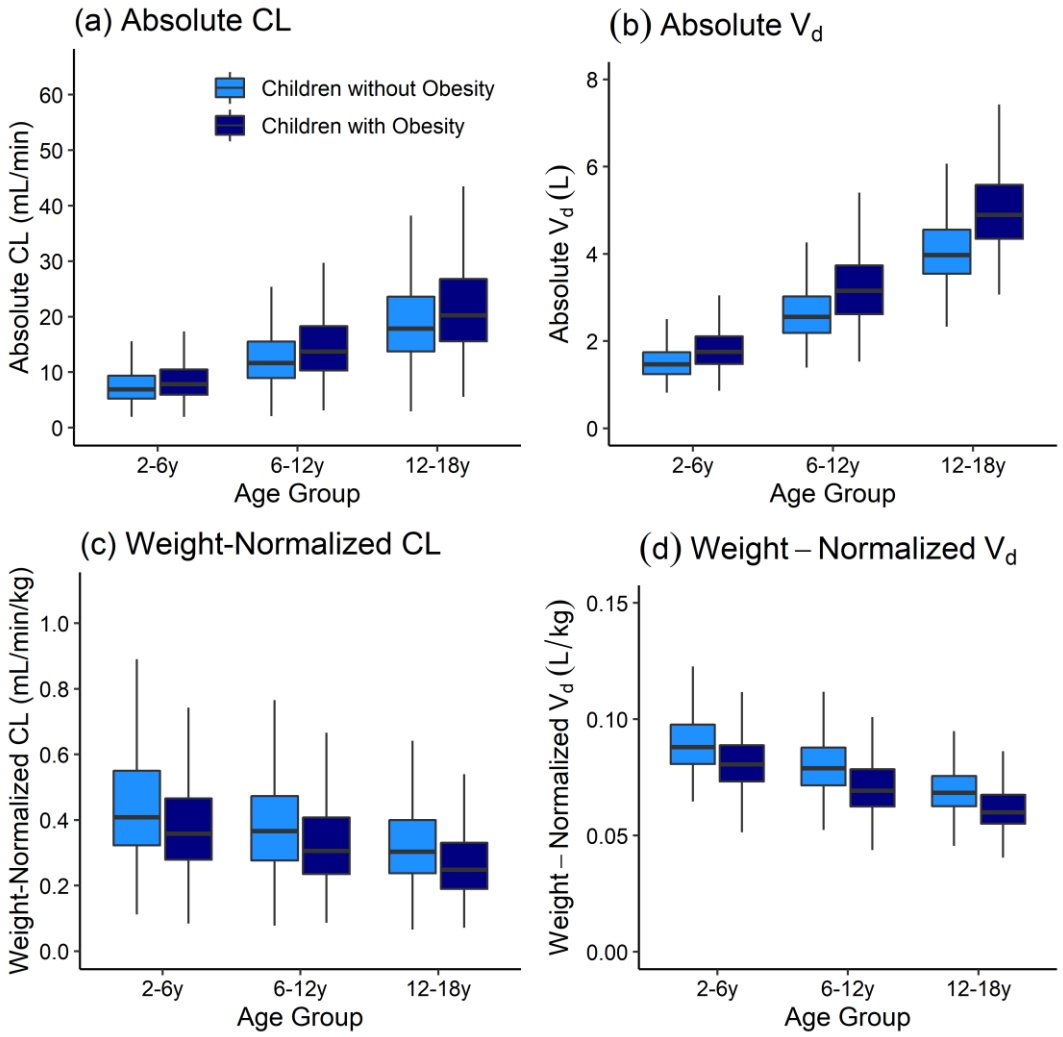
- ↑ Liver clearance
- ↔ Metabolism

1 Real world dataset | 2 **Model development** | 3 Dosing simulations

AAG: α1-acid glycoprotein
PBPK: physiologically-based pharmacokinetic

Gerhart et al. *Clin Pharmacokinet*. 2021.

PBPK model-estimated changes in enoxaparin disposition with obesity



1 Real world dataset

2 Model development

3 **Dosing simulations**

CL: clearance
PBPK: physiologically-based pharmacokinetic
V_d: volume of distribution

Gerhart et al. *Clin Pharmacol Ther.* 2022.