SUPPLEMENTARY MATERIAL

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

Running title: Real-World Data and PBPK Modeling of Enoxaparin 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

[1]Division of Pharmacotherapy and Experimental Therapeutics, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]School of Pharmacy, University of Waterloo, Waterloo, ON, Canada; School of Medicine, [3]Department of Pediatrics, UNC School of Medicine, The University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [4]Duke Clinical Research Institute, Durham, NC, USA; [5]Department of Pediatrics, Duke University School of Medicine, Durham, NC, USA; [6]Centre for Medicine Use and Safety, Monash University, Victoria, Australia.

Address correspondence to: Daniel Gonzalez, UNC Eshelman School of Pharmacy, The University of North Carolina at Chapel Hill, Campus Box #7569, Chapel Hill, NC 27599-7569, USA. Tel: +1-919-966-9984; Fax: +1-919-962-0644; E-mail: daniel.gonzalez@unc.edu.

TABLE OF CONTENTS

1 SUPPLEMENTARY FIGURES

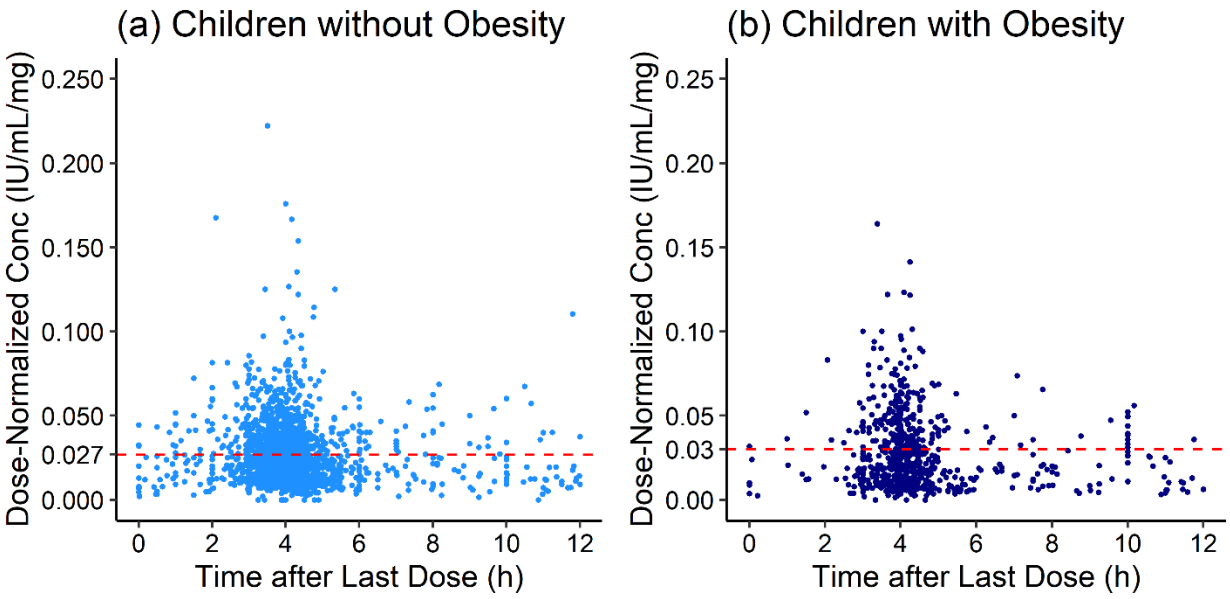

Figure S1. Anti-Xa dose-normalized concentration versus time after last dose for children without (a) and with (b) obesity. Dashed lines represent the mean dose-normalized anti-Xa 4-hour concentration.

Conc, concentration; IU, international unit

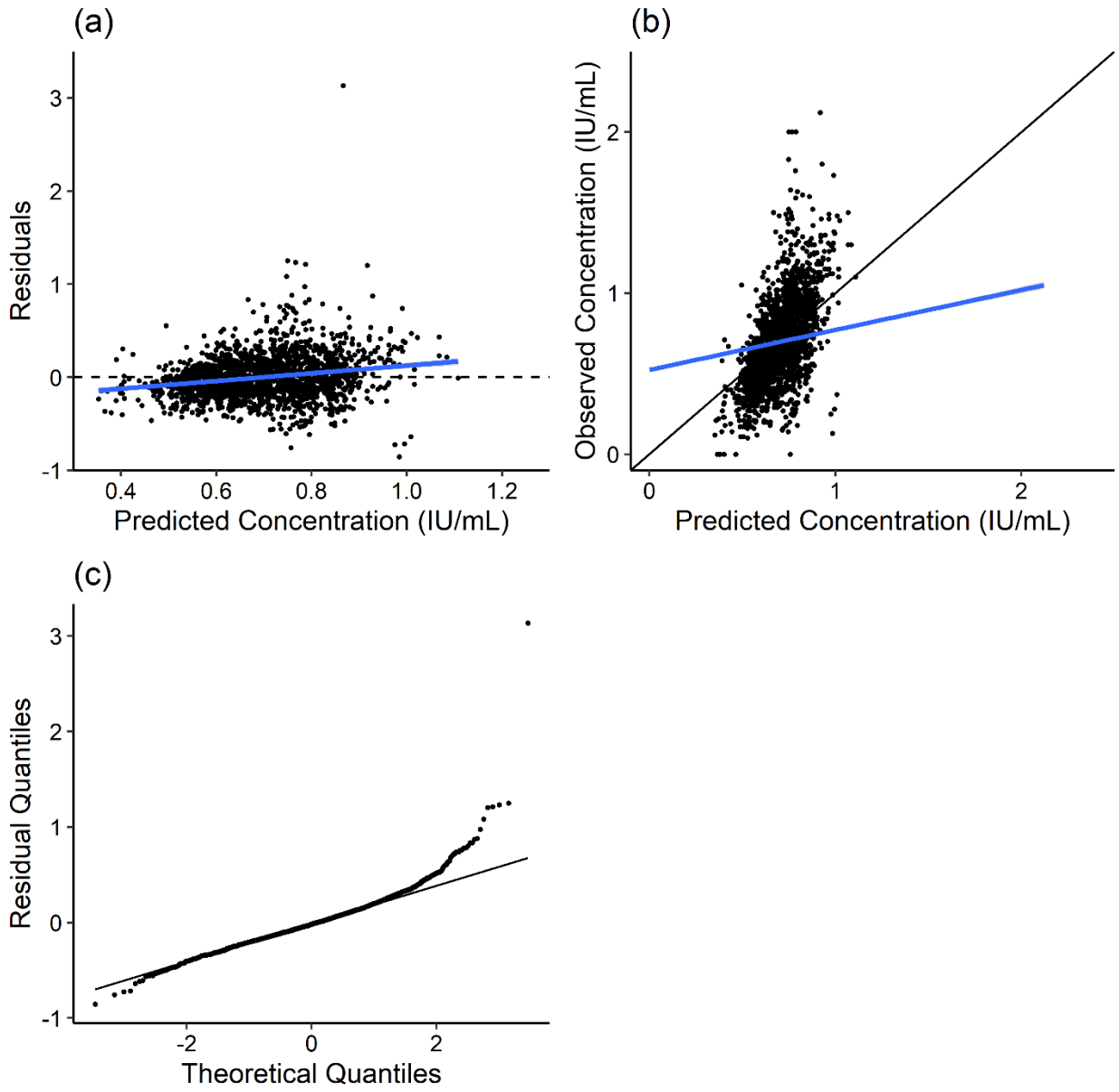

Figure S2. Residual (a), individual predicted versus observed concentration (b), and quantile-quantile (c) evaluation plots for a linear mixed-effects regression model of variables on anti-Xa 4-hour concentration for children receiving enoxaparin for treatment.

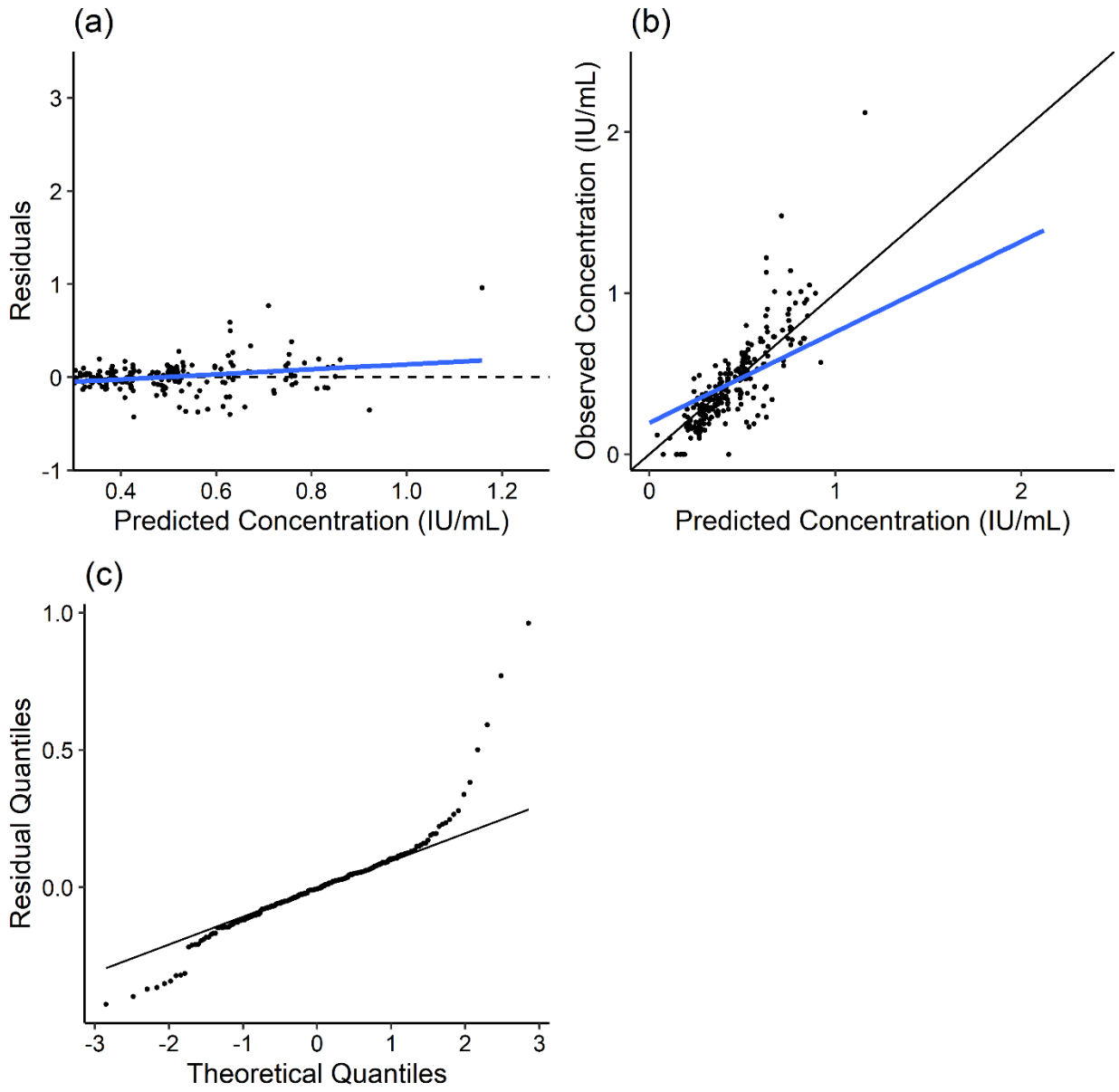

Figure S3. Residual (a), individual predicted versus observed concentration (b), and quantile-quantile (c) evaluation plots for a linear mixed-effects regression model of variables on anti-Xa 4-hour concentration for children receiving enoxaparin for prophylaxis.

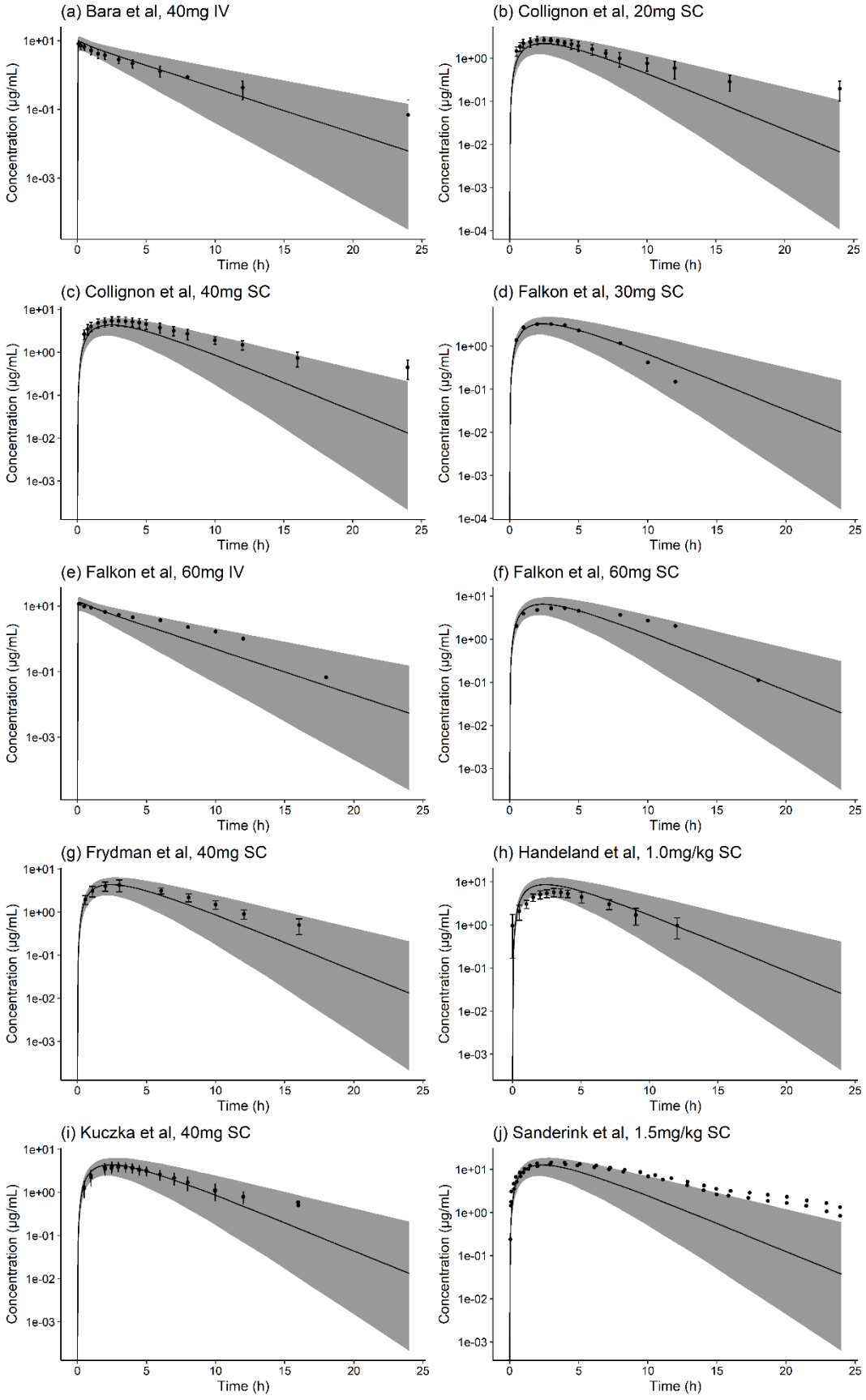
(a) Bara et al, 40mg IV
(b) Collignon et al, 20mg SC
(c) Collignon et al, 40mg SC
(d) Falkon et al, 30mg SC
(e) Falkon et al, 60mg IV
(f) Falkon et al, 60mg SC
(g) Frydman et al, 40mg SC
(h) Handeland et al, 1.0mg/kg SC
(i) Kuczka et al, 40mg SC
(j) Sanderink et al, 1.5mg/kg SC
Concentration (µg/mL)
Time (h)

Figure S4. PBPK model population simulations (n = 500) of enoxaparin concentrations digitized from adult studies. Shaded regions represent the 90% model prediction interval, and points are digitized observed enoxaparin concentrations with corresponding standard deviation values when available.

IV, intravenous; PBPK, physiologically-based pharmacokinetic; SC, subcutaneous

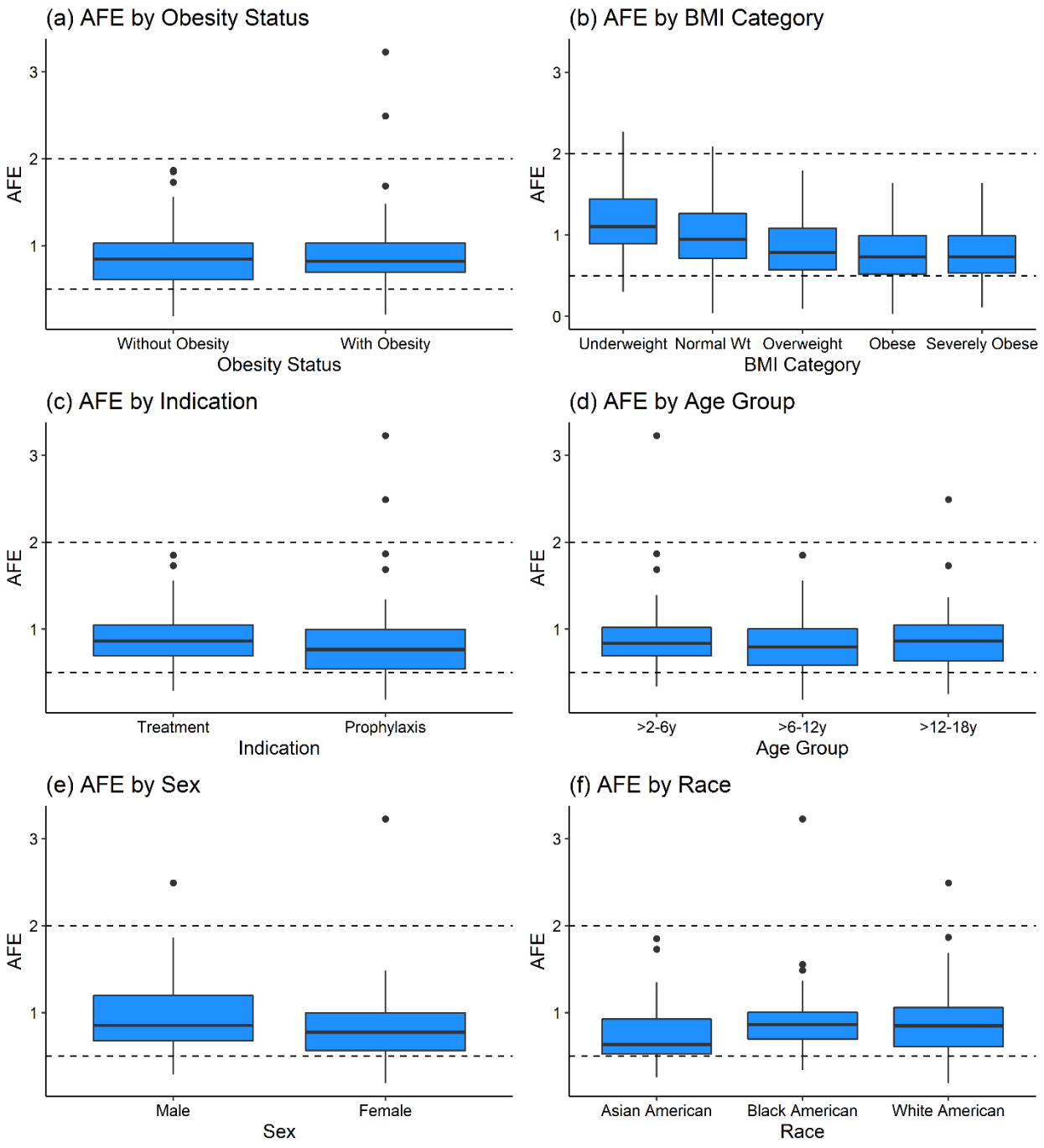

Figure S5. PBPK model AFE for pediatric participants from the real-world dataset versus obesity status, indication, age group, sex, and race. Dashed lines represent 2-fold error for reference. AFE was calculated using median simulated concentration. Boxes represent the median and IQR, and whiskers extend to 1.5 × IQR with further outlying values represented as points. For panel (b), children with underweight, normal weight, overweight, obesity, and severe

obesity were defined as having a BMI percentile of < 5%, ≥ 5% to 85%, ≥ 85% to 95%, ≥ 95% to 99%, and ≥ 99%, respectively.

AFE, average fold error; BMI, body mass index; IQR, interquartile range; PBPK, physiologically-based pharmacokinetic; Wt, weight

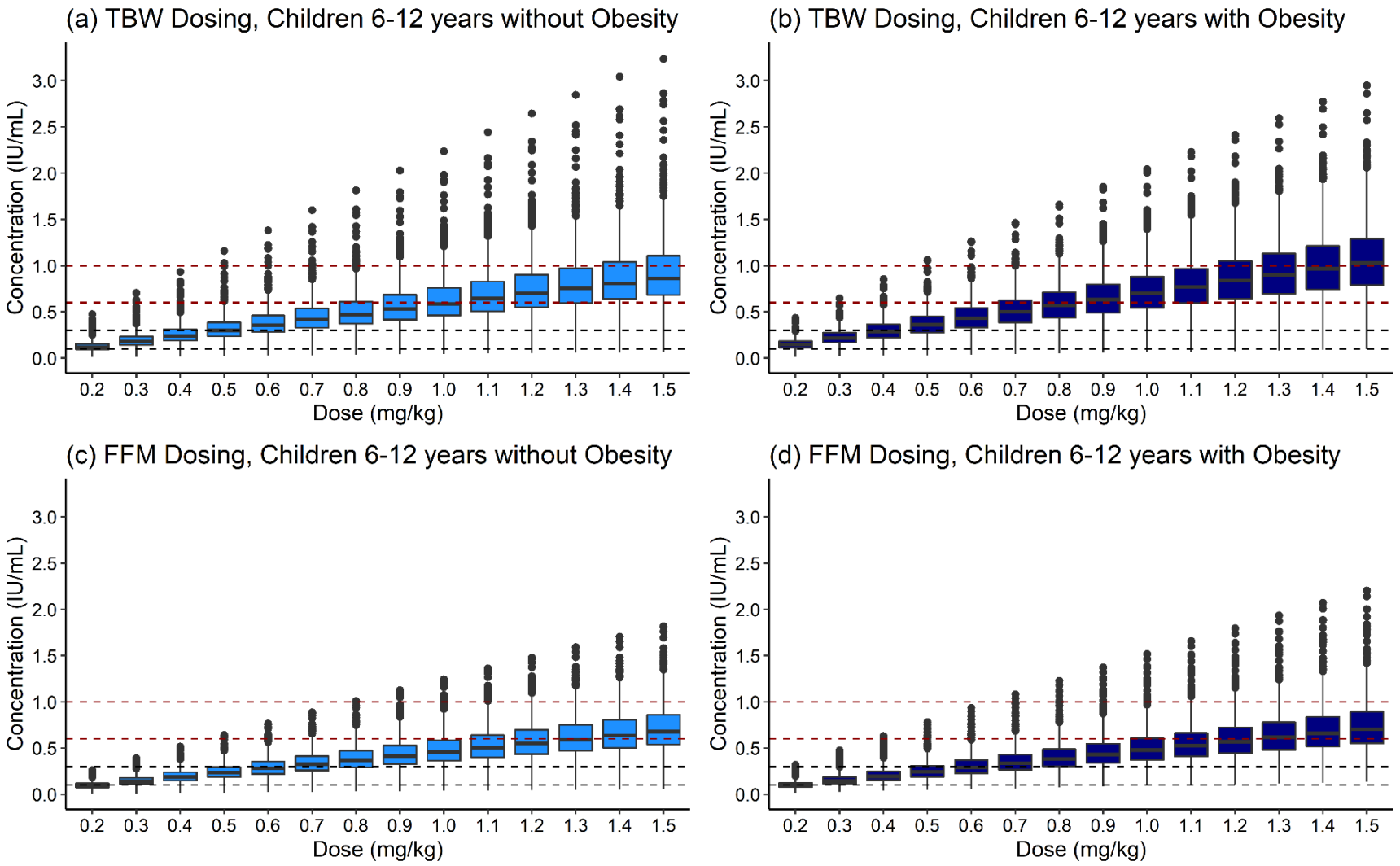

Figure S6. PBPK model simulated anti-Xa 4-hour concentration following twice-daily subcutaneous dosing of 0.2–1.5 mg/kg using TBW (a–b) or FFM (c–d) for children ages 6 to < 12 years without (a, c) and with (b, d) obesity (n= 1,000 children per group). Boxes

represent the median and IQR, and whiskers extend to 1.5 × IQR. Red and black dashed lines represent the target ranges for treatment (0.6–1.0 IU/mL) and prophylaxis (0.1–0.3 IU/mL) dosing, respectively.[1,2]

FFM, fat-free mass; PBPK, physiologically-based pharmacokinetic; TBW, total body weight

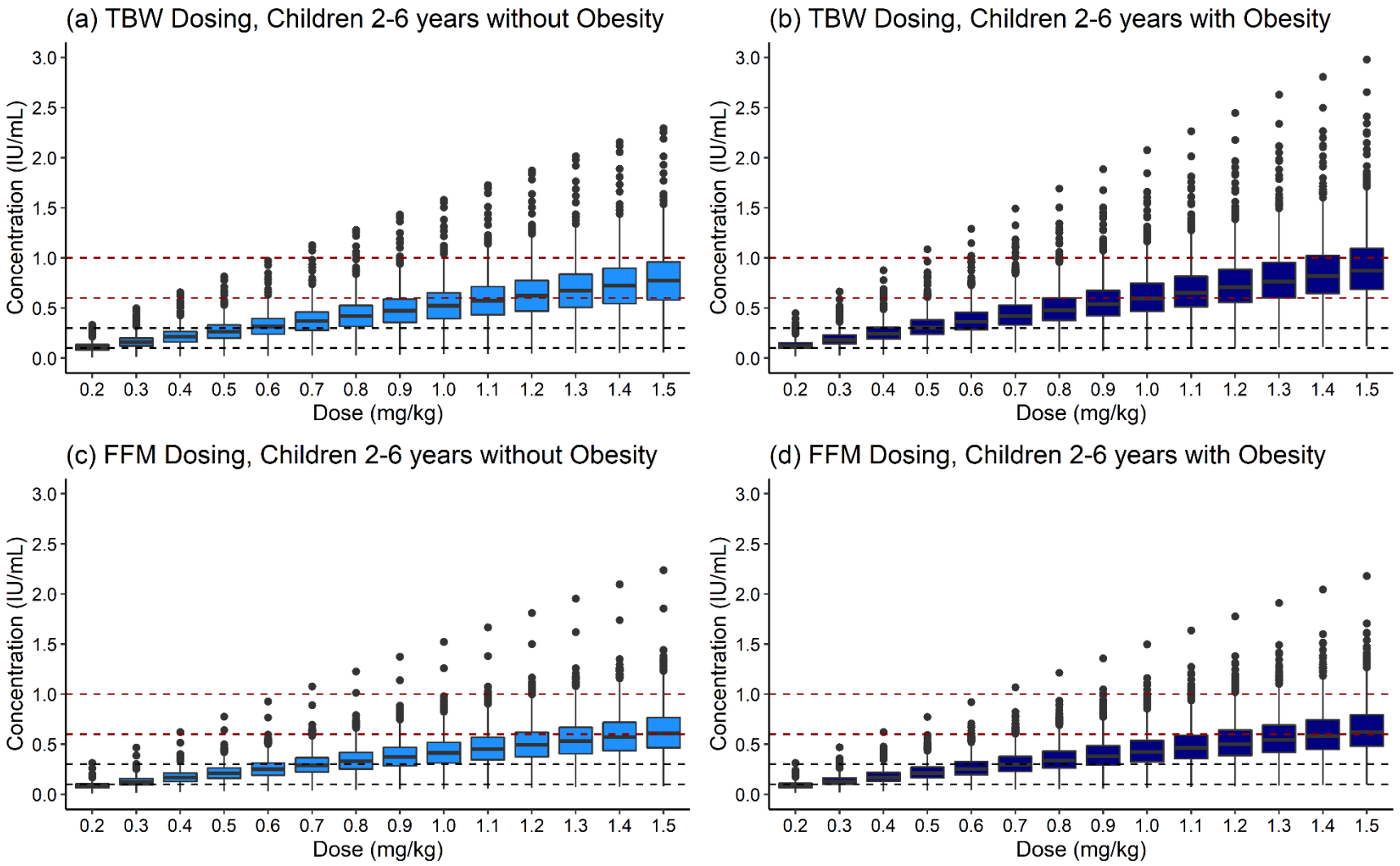

Figure S7. PBPK model simulated anti-Xa 4-hour concentration following twice-daily subcutaneous dosing of 0.2–1.5 mg/kg using TBW (a–b) or FFM (c–d) for children ages 2 to < 6 years without (a, c) and with (b, d) obesity (n = 1,000 children per group). Boxes

represent the median and IQR, and whiskers extend to 1.5 × IQR. Red and black dashed lines represent the target ranges for treatment (0.6–1.0 IU/mL) and prophylaxis (0.1–0.3 IU/mL) dosing, respectively.[1,2]

FFM, fat-free mass; PBPK, physiologically-based pharmacokinetic; TBW, total body weight

2 SUPPLEMENTARY TABLES

Table S1. Exclusion criteria applied to the real-world dataset of children receiving enoxaparin.

Starting participant count = 1,540	
Exclusion Criteria	**N, Excluded**
On VAD	4
On ECMO	19
On dialysis	23
Neoplasm diagnosis	158
No height recorded	286
No anti-Xa concentration recorded	378
Only baseline sample(s)	13
Extended TALD samples (> 80 hours)	18
Implausible height or BMI record	45
Ending participant count = 596	

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; TALD, time after last dose; VAD, ventricular assist device

Table S2. Comparison of site distribution, laboratory measures, and concomitant medications for children with versus without obesity receiving enoxaparin for treatment.

Parameter [a]	**Children *without* Obesity (*n = 415*)**	**Children *with* Obesity (*n = 104*)**	**P-value** [b]
SITE			
Site 1	86 (20.7%)	24 (23.1%)	0.31
Site 2	210 (50.6%)	47 (45.2%)	
Site 3	53 (12.8%)	19 (18.3%)	
Site 4	13 (3.1%)	6 (5.8%)	
Site 5	30 (7.2%)	4 (3.8%)	
Site 6	23 (5.5%)	4 (3.8%)	
LABORATORY MEASURES			
Hemoglobin (g/dL)	11.3 (2.0) (7.5%)	11.1 (2.0) (9.6%)	0.31
Hematocrit (%)	33.8 (5.8) (7.5%)	33.7 (5.5) (9.6%)	0.66
Platelets (thousands/μL)	281 (145) (7.7%)	274 (149) (9.6%)	0.997
INR	1.27 (0.32) (26.7%)	1.24 (0.25) (37.5%)	0.33
BUN (mg/dL)	13.5 (7.9) (10.6%)	14.4 (10.0) (37.5%)	0.57
Serum creatinine (mg/dL)	0.49 (0.36) (10.4%)	0.51 (0.28) (13.5%)	0.38
$CL_{creatinine}$ (mL/minute/1.73m^2) [c]	138.1 (51.5) (10.1%)	123.2 (37.0) (12.5%)	**0.001 ***
Absolute $CL_{creatinine}$ (mL/minute) [d]	84.0 (41.2) (10.1%)	90.8 (45.9) (12.5%)	0.07
Total bilirubin (mg/dL)	0.77 (0.96) (30.1%)	0.69 (0.0.53) (41.3%)	0.43
Direct bilirubin (mg/dL)	0.53 (1.00) (65.3%)	0.30 (0.31) (75.0%)	0.06

Indirect bilirubin (mg/dL)	0.41 (0.54) (75.9%)	0.33 (0.45) (85.6%)	0.42
CONCOMITANT MEDICATIONS			
Aspirin	96 (22.6%)	25 (21.0%)	0.39
Bivalirudin	5 (1.2%)	1 (0.8%)	1.00
Heparin	162 (38.1%)	27 (22.7%)	0.27
Rivaroxaban	2 (0.4%)	0 (0%)	1.00
Steroids	146 (34.4%)	50 (42.0%)	0.09
Warfarin	51 (12.0%)	10 (8.4%)	0.31

* Statistically significant at the $\alpha = 0.05$ level.

[a] Summary statistics are reported as mean (standard deviation) (% missing) for continuous variables and as count (%) for categorical variables. Laboratory measure summary statistics were calculated using each participant's average value across all encounters. Concomitant medications were tallied if the participant experienced it during any encounter.

[b] Continuous variables were compared using Welch's t-tests, while categorical variables were compared using Pearson's χ^2 tests. A p-value < 0.05 is considered statistically significant. The results were similar when using Mann-Whitney U/Wilcoxon rank-sum tests, after testing for normality using Shapiro-Wilk, Kolmogorov-Smirnov, and Levene's tests (results not shown).

[c] Estimated by the Bedside Schwartz equation (creatinine clearance = 0.41 × height [cm] / serum creatinine [mg/dL])

[d] Estimated by multiplying the estimated creatinine clearance by the Bedside Schwartz equation by BSA, as calculated by the Haycock equation (BSA = weight [kg] ^ 0.5378 × height [cm] ^ 0.3964 × 0.024265), then dividing by 1.73.

BUN, blood urea nitrogen; BSA, body surface area; $CL_{creatinine}$, creatinine clearance; INR, international normalized ratio; IQR, interquartile range

Table S3. Comparison of site distribution, laboratory measures, and concomitant medications for children with versus without obesity receiving enoxaparin for prophylaxis.

Parameter [a]	**Children *without* Obesity (*n = 78*)**	**Children *with* Obesity (*n = 41*)**	**P-value** [b]
SITE			
Site 1	15 (19.2%)	15 (36.6%)	0.08
Site 2	34 (43.6%)	12 (29.3%)	
Site 3	4 (5.1%)	6 (14.6%)	
Site 4	3 (3.8%)	2 (4.9%)	
Site 5	14 (17.9%)	3 (7.3%)	
Site 6	8 (10.3%)	3 (7.3%)	
LABORATORY MEASURES			
Hemoglobin (g/dL)	10.8 (2.0) (7.7%)	10.7 (1.7) (7.3%)	0.60
Hematocrit (%)	32.2 (5.6) (7.7%)	32.3 (5.9) (7.3%)	0.89
Platelets (thousands/μL)	268 (117) (7.7%)	277 (149) (7.3%)	0.76
INR	1.21 (0.16) (41.0%)	1.25 (0.29) (51.2%)	0.83
BUN (mg/dL)	13.6 (6.9) (6.4%)	18.1 (18.0) (7.3%)	0.09
Serum creatinine (mg/dL)	0.51 (0.41) (6.4%)	0.72 (0.51) (7.3%)	**< 0.01 ***
$CL_{creatinine}$ (mL/minute/1.73m^2) [c]	153.5 (89.0) (6.4%)	113.7 (48.9) (7.3%)	**< 0.001 ***
Absolute $CL_{creatinine}$ (mL/minute) [d]	106.8 (78.4) (6.4%)	113.1 (58.4) (7.3%)	0.40
Total bilirubin (mg/dL)	0.79 (0.92) (23.1%)	0.96 (2.15) (34.1%)	0.64
Direct bilirubin (mg/dL)	0.57 (1.20) (62.8%)	0.87 (1.62) (85.4%)	0.52

Indirect bilirubin (mg/dL)	0.31 (0.32) (74.4%)	0.67 (0.59) (92.7%)	0.16
CONCOMITANT MEDICATIONS			
Aspirin	21 (26.3%)	15 (31.9%)	0.29
Bivalirudin	0 (0%)	0 (0%)	---
Heparin	19 (23.8%)	12 (25.5%)	0.99
Rivaroxaban	0 (0%)	0 (0%)	---
Steroids	31 (38.8%)	21 (44.7%)	1.00
Warfarin	5 (6.3%)	4 (8.5%)	1.00

* Statistically significant at the $\alpha = 0.05$ level.

[a] Summary statistics are reported as mean (standard deviation) (% missing) for continuous variables and as count (%) for categorical variables. Laboratory measure summary statistics were calculated using each participant's average value across all encounters. Concomitant medications were tallied if the participant experienced it during any encounter.

[b] Continuous variables were compared using Welch's t-tests, while categorical variables were compared using Pearson's χ^2 tests. A p-value < 0.05 is considered statistically significant. The results were similar when using Mann-Whitney U/Wilcoxon rank-sum tests, after testing for normality using Shapiro-Wilk, Kolmogorov-Smirnov, and Levene's tests (results not shown).

[c] Estimated by the Bedside Schwartz equation (creatinine clearance = 0.41 × height [cm] / serum creatinine [mg/dL])

[d] Estimated by multiplying the estimated creatinine clearance by the Bedside Schwartz equation by BSA, as calculated by the Haycock equation (BSA = weight [kg] ^ 0.5378 × height [cm] ^ 0.3964 × 0.024265), then dividing by 1.73.

BUN, blood urea nitrogen; BSA, body surface area; $CL_{creatinine}$, creatinine clearance; INR, international normalized ratio; IQR, interquartile range

Table S4. Population demographics for simulated participants with and without obesity who were used in enoxaparin PBPK model dosing simulations.

Demographics	Children without Obesity	Children with Obesity [a]
Age (years)	8.9 (2.0, 18.0)	9.0 (2.0, 18.0)
Age group		
≥ 2 and < 6 years	1,000 (33.3%)	1,000 (33.3%)
≥ 6 and < 12 years	1,000 (33.3%)	1,000 (33.3%)
≥ 12 years	1,000 (33.3%)	1,000 (33.3%)
Weight (kg)	32.1 (9.5, 102.5)	45.1 (10.6, 179.1)
Height (cm)	135.8 (76.8, 200.2)	135.6 (74.4, 200.1)
BMI (kg/m^2)	17.6 (11.5, 29.7)	24.9 (17.9, 65.8)
BMI percentile (%)	68.3 (0, < 95.0)	98.1 (95.0 100.0)
Extended BMI (%)	83.3 (53.0, < 100.0)	110.5 (100.0, 236.4)
Male	1,500 (50.0%)	1,500 (50.0%)

Values are medians (range) for continuous variables and counts (%) for categorical variables. Extended BMI is calculated as the participant's BMI divided by the 95^{th} BMI percentile for a participant's age and sex, where children with an extended BMI ≥100% are considered obese.

[a] Simulated children with obesity were generated using a virtual population with increased overall body weight as determined by updated BMI-for-age growth curves and increased lean body weight, organ volume, blood flow, and corresponding effects on clearance processes as previously described.[3]

BMI, body mass index; PBPK, physiologically-based pharmacokinetic

Table S5. Parameters for a linear mixed-effects regression model regressing anti-Xa 4-hour concentration onto key variables for children receiving enoxaparin for prophylaxis.[a]

Parameter	Estimate [b]	95% CI
Intercept (IU/mL)	0.33	**(0.22, 0.44) ***
Age (years)	-0.11	**(-0.16, -0.06) ***
Absolute dose (mg)	0.25	**(0.19, 0.30) ***
Extended BMI (%)	-0.002	(-0.05. 0.05)
Ethnicity – Not Hispanic	0.07	(-0.04. 0.18)
$CL_{creatinine}$ (mL/minute/1.73m^2)	-0.03	(-0.07, 0.01)
Absolute dose * Extended BMI	-0.06	**(-0.09. -0.02) ***

* Statistically significant at the $\alpha = 0.05$ level.

[a] The regression model was developed using the R packages "lme4", "mice", and "broom.mixed".[4–6]

[b] Variables were centered on the median value and scaled by the standard deviation. A random slope was fitted for each participant and site. Missing $CL_{creatinine}$ values were imputed using a predictive mean matching multiple imputation method.

BMI, body mass index; CI, confidence interval; $CL_{creatinine}$, creatinine clearance

Table S6. Population demographics and PBPK model simulation results for digitized adult enoxaparin studies.

Demographics	Value
Bara *et al* (1985) [7]	
Patient population	Healthy volunteers
N	8
Age (years)	(21–29)
Weight (kg)	70.7 ± 4
Male	8 (100%)
Dose	40 mg IV bolus
Anti-Xa assay	Amidolytic
PK parameters, Reported; Observed (% error) $t_{1/2}$ (hours) Cl (mL/minute) AUC (mg*minute/mL) C_{max} (μg/mL) Bioavailability (%)	 4.6; 2.3 (50.0%) 24.2; 25.6 (5.8%) 1.16; 1.53 (31.9%) 5.5; 9.2 (67.3%) 91; 98 (7.7%)
AFE	0.89
Collignon *et al* (1995) [8]	
Patient population	Healthy volunteers
N	20
Age (years)	(18–30)
Weight (kg)	(65–92.4)
Male	20 (100%)
Dose	20 mg SC 40 mg SC
Anti-Xa assay	Amidolytic
PK parameters, Reported; Observed (% error)	

$t_{1/2}$ (hours)	
20 mg	3.95; 2.34 (40.8%)
40 mg	4.37; 2.33 (46.7%)
Cl/F (mL/minute)	
20 mg	16.67; 25.0 (50.0%)
40 mg	13.83; 25.2 (82.2%)
AUC (mg*minute/mL)	
20 mg	1.18; 0.80 (32.2%)
40 mg	2.74; 1.59 (42.0%)
t_{max} (hours)	
20 mg	2.35; 2.50 (6.4%)
40 mg	2.91; 2.50 (14.1%)
V_d/F (L)	
20 mg	5.50; 4.60 (16.4%)
40 mg	5.24; 4.64 (11.5%)
AFE	
20 mg	0.58
40 mg	0.52
Falkon *et al* (1995) [9]	
Health status	Healthy volunteers
N	12
Age (years)	28.4 ± 2.4
Weight (kg)	76.3 ± 8.9
Male	12 (100%)
Dose	60 mg IV bolus 30 mg SC 60 mg SC
Anti-Xa assay	Amidolytic
PK parameters, Reported; Observed (% error)	
k_a (1/hours)	

30 mg SC	1.2; 0.6 (50.0%)
60 mg SC	0.63; 0.60 (0%)
$t_{1/2}$ (hours)	
60 mg IV bolus	2.5; 2.1 (16.0%)
30 mg SC	5.3; 2.3 (56.6%)
60 mg SC	5.29; 2.34 (55.8%)
AUC (mg*minute/mL)	
60 mg IV bolus	3.01; 2.30 (23.6%)
30 mg SC	1.21; 1.20 (0.8%)
60 mg SC	2.82; 2.35 (16.7%)
C_{max} (µg/mL)	
60 mg IV bolus	13.0; 12.9 (0.8%)
30 mg SC	3.4; 3.3 (2.9%)
60 mg SC	5.4; 6.5 (20.4%)
t_{max} (hours)	
60 mg IV bolus	0.05; 0.15 (200.0%)
30 mg SC	2–3; 2.5
60 mg SC	3–4; 2.3
V_d (L)	
60 mg IV bolus	5.1; 4.7 (7.8%)
Bioavailability (%)	
30 mg	81.1; 98.0 (20.8%)
60 mg	95.6; 99.0 (1.0%)
AFE	
60 mg IV bolus	0.67
30 mg SC	1.11
60 mg SC	0.87
Frydman *et al* (1996) [10]	
Patient population	Healthy volunteers
N	41
Age (years)	NR

Weight (kg)	NR
Male	NR
Dose	40 mg SC
Anti-Xa assay	NR
PK parameters Reported; Observed (% error) $t_{1/2}$ (hours)	5.2; 2.3 (55.8%)
AFE	0.72
Handeland *et al* (1990) [11]	
Patient population	Deep venous thromboembolism patients
N	15
Age (years)	(20–90)
Weight (kg)	(48–90)
Male	6 (40%)
Dose	1.0 mg/kg SC
Anti-Xa assay	Chromogenic
PK parameters, Reported; Observed (% error) $t_{1/2}$ (hours)	3.0; 2.3 (23.3%)
AFE	0.95
Kuczka *et al* (2008) [12]	
Patient population	Healthy volunteers
N	20
Age (years)	(27–37)
Weight (kg)	(66–90)
Male	10 (50%)
Dose	40 mg SC
Anti-Xa assay	Chromogenic
PK parameters, Reported; Observed (% error)	

AUC (mg*minute/mL)	1.60; 1.59 (0.6%)
C_{max} (μg/mL)	3.9; 4.4 (12.8%)
t_{max} (hours)	3.1; 2.5 (19.4%)
AFE	0.91
Sanderink *et al* (2002) [13]	
Patient population	Healthy volunteers
N	24
Age (years)	(18–50)
Weight (kg)	(50.3–82.1)
Male	12 (50%)
Dose	1.5 mg/kg SC
Anti-Xa assay	Chromogenic
PK parameters, Reported; Observed (% error)	
$t_{1/2}$ (hours)	4.85; 2.33 (52.0%)
AUC (mg*minute/mL)	8.92; 5.02 (43.7%)
C_{max} (μg/mL)	13.44; 8.63 (35.8%)
t_{max} (hours)	3.5; 2.3 (34.3%)
AFE	0.30

Values shown as mean ± standard deviation (range).

AFE, average fold error; AUC, area under the concentration-versus-time curve; Cl, clearance; Cl/F, apparent subcutaneous clearance; C_{max}, maximum concentration; IV, intravenous; k_a, absorption rate constant; NR, not reported; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; SC, subcutaneous; $t_{1/2}$, half-life; t_{max}, time of maximum concentration; V_d, volume of distribution; V_d/F, apparent subcutaneous volume of distribution

Table S7. Mean simulated clearance in virtual adults receiving SC and IV administration of enoxaparin is dose linear.

Dose (mg)	**Simulated Clearance following SC Administration (mL/minute)**	**Simulated Clearance following IV Administration (mL/minute)**	**Bioavailability (%)**
20	23.4	22.9	97.6
30	23.6	23.1	97.9
40	23.7	23.3	98.1
60	23.9	23.6	98.8
≈ 80 (1 mg/kg)	24.2	24.0	99.4
≈ 120 (1.5 mg/kg)	24.7	24.8	100.0

Note that the FDA label reported clearance in adults following SC and IV administration is 15 and 26 mL/minute, respectively.[14]

IV, intravenous; SC, subcutaneous

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