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# Clinical Experience With Prophylactic Fondaparinux in Critically Ill Patients With Moderate to Severe Renal Impairment or Renal Failure Requiring Renal Replacement Therapy

**Jessica Cope, PharmD[1], Jennifer Bushwitz, PharmD[2], Guohua An, MD[3], Abigail Antigua, PharmD[1], Anjan Patel, MD[4], and Marc Zumberg, MD[4]**

## Abstract

**Background:** Fondaparinux has an increased bleeding risk in patients with a CrCl ≤ 50 mL/min and is contraindicated if CrCl < 30 mL/min. Data regarding dosing and anti-Xa monitoring are lacking in this population. **Objective:** To describe dosing, monitoring, and safety outcomes of prophylactic fondaparinux in critically ill patients with moderate to severe renal impairment, including renal replacement therapy (RRT). **Methods:** Retrospective analysis from October 2006 to November 2012 of patients ≥ 18 years old who received fondaparinux for ≥ 72 hours with ≥ 1 dose in an intensive care unit and a CrCl ≤ 50 mL/min or RRT during therapy. Participants were divided into 4 cohorts: moderate impairment (CrCl = 30-50 mL/min), severe impairment (CrCl < 30 mL/min), hemodialysis (HD), or continuous venovenous hemofiltration (CVVH). Outcomes included the incidence of clinically significant bleeding and thromboembolic events. Fondaparinux dose, dosing frequency, and anti-Xa level monitoring are described. Pharmacokinetic modeling was performed to assess drug accumulation. **Results:** In all, 95 patients met inclusion criteria: 64 (67.4%) with moderate impairment, 10 (10.5%) with severe impairment, 5 (5.3%) with HD, and 16 (16.8%) with CVVH. The median defined daily doses in the moderate, severe, HD, and CVVH cohorts were 2.5, 2.5, 0.9, and 1.9 mg. Anti-Xa monitoring occurred in 19 (20%) patients, although few concentrations were peaks. Clinically significant bleeding occurred in 4 (4.2%) patients. A pharmacokinetic model demonstrated drug accumulation. **Conclusions:** Empirical dose adjustments may be prudent in critically ill patients with renal dysfunction; however, the optimal fondaparinux dosage in this population remains unknown. Peak anti-Xa concentrations may help guide therapy.

**Keywords**

fondaparinux, renal impairment, dialysis, anti-Xa monitoring, major bleeding, heparin-induced thrombocytopenia

## Background

Prevention of venous thromboembolism (VTE) in critically ill patients is challenging. Renal impairment, which has been identified as a risk factor for both bleeding and venous thromboembolism, is common.[1,2] Fondaparinux, a selective Factor-Xa inhibitor used for the treatment and prevention of venous thromboembolism, is primarily renally eliminated.[3] Data regarding safe and effective use in critically ill patients with renal impairment are lacking. This lack of data may place patients at increased risk for bleeding secondary to fondaparinux accumulation or thromboembolism as a result of underdosing.[4]

Per the manufacturer, caution is warranted when administering fondaparinux to patients with a creatinine clearance (CrCl) of 30 to 50 mL/min; however, dose modifications are not specifically recommended.[5] Recently, experts recommended considering a 40% dose reduction in patients with a CrCl of 20 to 50 mL/min receiving fondaparinux for VTE prophylaxis and suggest anti-Xa monitoring to help guide therapy.[6] Fondaparinux use as VTE prophylaxis is also contraindicated by the manufacturer in patients with a CrCl < 30 mL/min or those weighing < 50 kg.[5] Data in these

[1]UF Health Shands Hospital, Gainesville, FL, USA
[2]Barnes-Jewish Hospital, St Louis, MO, USA
[3]University of Florida, Orlando, FL, USA
[4]University of Florida College of Medicine, Gainesville, FL, USA

**Corresponding Author:**
Jessica Cope, Critical Care, Department of Pharmacy, UF Health Shands Hospital, 1600 SW Archer Blvd, Gainesville, FL 32610, USA.
Email: copej@shands.ufl.edu

patients and those with renal failure requiring renal replacement therapy (RRT) are limited to case reports and small case series.[7-11] Dosing recommendations, therefore, are largely based on expert opinion, and clinical practice is variable.[5,11]

We report the use of fondaparinux for the prevention of VTE at our institution, a 939-bed academic medical center with approximately 140 intensive care unit (ICU) beds, in critically ill patients with moderate to severe renal impairment, including those receiving RRT. Our institution has six adult critical care units, including medical, cardiothoracic, neurosurgical, general surgery, burn surgery, and trauma ICUs. The purpose of this study was to describe fondaparinux dosing, monitoring, and safety outcomes in this population. A population pharmacokinetic analysis was conducted to further investigate fondaparinux exposure.

## Material and Methods

### Study Design

We conducted a retrospective, observational analysis of critically ill adult patients with moderate to severe renal impairment receiving fondaparinux for the prevention of VTE. Patients admitted between October 1, 2006, and November 30, 2012, who were charged for fondaparinux and had an ICD-9 diagnosis or procedure code or a CPT (Current Procedural Terminology) code signifying renal impairment or RRT were screened for inclusion (supplementary Appendix A). Participants were included if they had been prescribed fondaparinux for VTE prophylaxis, had received at least one dose of fondaparinux in an ICU, had received fondaparinux for at least 72 hours, and had a CrCl ≤ 50 mL/min or received RRT concurrently. Renal impairment was validated by calculating a daily CrCl, using the Cockcroft and Gault equation, for all patients while on therapy. An adjusted body weight was used to calculate daily CrCl for those whose weight was greater than their ideal body weight (IBW), whereas actual body weight was used for those weighing less than their IBW.[12]

Pharmacy charge data were used to identify fondaparinux dose, dosing interval, and duration of therapy. Anti-Xa serum concentrations and serum creatinine were obtained from our institution's laboratory database. To assess the dosing and monitoring regimens utilized, patients were divided into four mutually exclusive categories: moderate renal impairment (CrCl = 30-50 mL/min), severe renal impairment (CrCl < 30 mL/min), receiving hemodialysis (HD), or on continuous venovenous hemofiltration (CVVH). For those who qualified for more than one group, placement was defined by the majority of time spent in one category while receiving fondaparinux. To assess trends in the use of anti-Xa monitoring, characteristics of those who did and did not undergo therapeutic drug monitoring were compared.

### Objectives

Our primary objective was to describe the dosing and monitoring strategies observed in patients receiving prophylactic fondaparinux with a CrCl ≤ 50 mL/min. For ease of comparison, fondaparinux regimens are described using a defined daily dose. Additionally, we sought to describe the incidence of clinically significant bleeding, thromboembolic events, incidence of suspected and confirmed heparin-induced thrombocytopenia (HIT), fondaparinux indication for use, use of our hematology consult service, and hospital and ICU length of stay (LOS). Bleeding and thromboembolic events were identified via previously validated ICD-9 diagnosis codes found in supplementary Appendices B and C.[13] Events identified via ICD-9 coding were reviewed and validated by the primary investigator and a hematology fellow. Only new, clinically significant bleeding and thromboembolic events were included.

### Definitions

Defined daily dose was the average dose received during a 24-hour period. Prophylactic and therapeutic fondaparinux peak anti-Xa ranges are defined as 0.39 to 0.5 µg/mL and 1.2 to 1.26 µg/mL, respectively (STA-Rotachrom, Diagnostica Stago).

Clinically significant bleeding was defined as follows: any patient with a related medical diagnosis code (supplementary Appendix B) experiencing a fatal bleed, symptomatic bleed in a critical area or organ (eg, intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, or pericardial), or receiving at least two units of packed red blood cells within 24 hours of the event.[14-19] Bleeding events were confirmed with radiographic imaging, including computed tomography, magnetic resonance imaging, esophagogastroduodenoscopy, and colonoscopy reports, in addition to reviewing patients' progress notes for event description.

A VTE event was defined as any new deep-vein thrombosis or pulmonary embolism in a patient with a related medical diagnosis code (supplementary Appendix C) and radiographic evidence of thrombosis on chart review. The diagnosis of VTE was made by Doppler ultrasound, venography, computed tomography, magnetic resonance imaging, ventilation-perfusion scan, or pulmonary angiography.

Suspected HIT was defined as any patient with a heparin platelet factor-4 (PF4) antibody result. Confirmed HIT was defined as a heparin PF4 antibody > 4 relative absorbance units and a serotonin release assay > 20% per our laboratory standards.

### Analysis

All research and analysis was approved by the University of Florida's institutional review board. Nominal variables

**Table 1.** Summary of Prophylactic Fondaparinux by Renal Impairment Category.[a]

| | Moderate (n = 64) | Severe (n = 10) | HD (n = 5) | CVVH (n = 16) |
|---|---|---|---|---|
| DDD, mg[b,c] | 2.5 (1.25-2.5) | 2.5 (1.25-2.5) | 0.9 (0.6-2.5) | 1.9 (0.6-2.5) |
| Dosing frequency, n (%) | | | | |
| Every 24 hours | 69 (94.5) | 8 (72.7) | 1 (16.7) | 19 (79.2) |
| Every 48 hours | 3 (4.1) | 3 (27.3) | 4 (66.7) | 5 (20.8) |
| Every 72 hours | 1 (1.4) | 0 | 0 | 0 |
| Posthemodialysis | 0 | 0 | 1 (16.7) | 0 |
| Duration, days[b] | 9 (3-61) | 4 (3-6) | 13 (3-28) | 4 (3-128) |
| Patients with anti-Xa monitoring, n (%) | 6 (9.4) | 2 (20) | 3 (60) | 8 (50) |
| Patients with at least 1 appropriately drawn anti-Xa concentration, n (%) | 5 (7.8) | 2 (20) | 3 (60) | 8 (50) |
| Regimens, n | 73 | 11 | 6 | 24 |
| Anti-Xa concentrations | 13 | 4 | 9 | 23 |
| Anti-Xa levels per patient[b,d] | 2 (1-5) | 2 | 3 (1-4) | 1 (1-11) |
| Time from previous dose to level, hours[b] | 5.3 (2.5-23) | 7.5 (3.5-46.5) | 4.3 (2-14) | 3 (2.5-23) |
| Doses administered prior to level, n[b] | 4 (2-13) | 1.5 (1-3) | 4 (2-13) | 7 (2-48) |
| Anti-Xa drawn 3-5 hours postdose, n (%) | 7 (53.8) | 2 (50) | 5 (55.6) | 15 (65) |
| All anti-Xa, μg/mL[b] | 0.5 (0.2-0.9) | 0.2 (0.1-0.5) | 0.4 (0.1-0.7) | 0.4 (0.2-1.0) |
| Peak anti-Xa, μg/mL[b] | 0.4 (0.2-0.8) | 0.4 (0.3-0.5) | 0.4 (0.1-0.7) | 0.5 (0.1-1.0) |

Abbreviations: CrCl, creatinine clearance; CVVH, continuous venovenous hemofiltration; DDD, defined daily dose; HD, hemodialysis.
[a]Moderate: CrCl = 30-50 mL/min; severe: CrCl < 30 mL/min.
[b]Median (range).
[c]Fondaparinux prescribed dose: 2.5 or 1.25 mg.
[d]Patients with anti-Xa concentrations only.

were compared using Pearson $\chi^2$ or Fisher's exact test. Continuous variables were analyzed using the Mann-Whitney *U* test. All analyses were conducted using SPSS (v22.0).

### *Population Pharmacokinetic (PK) Analysis*

Anti-Xa plasma data were analyzed using nonlinear mixed-effects modeling software NONMEM, version 7.2 (Icon Development Solutions, Ellicott City, Maryland). The first-order conditional estimation method with the interaction (FOCEI) and a user-defined subroutine (ADVAN6) were used to estimate the typical population PK parameters, random interindividual variability (IIV), and residual variability (RV) between observed and individually predicted plasma anti-Xa concentrations. Random IIV was considered to be log normal and described by an exponential model. The residual error was modeled using a combined additive and exponential random-effect model. Final PK model selection was based on the visual inspection of goodness-of-fit plots, the objective function value, and the precision of parameter estimation. The likelihood ratio test was used for comparing nested models. A drop of 3.84 or more in the objective function value was considered significant.

Anti-Xa was described by a two-compartment model with first-order absorption and first-order elimination from the central compartment. The anti-Xa PK model was parameterized in terms of a first-order absorption rate constant ($K_a$), apparent volume of distribution of the central compartment (Vp), apparent volume of distribution of the peripheral compartment (Vt), distribution clearance (*Q*), and apparent clearance (CL).

Based on the pharmacokinetic parameters obtained from the final model, model simulation was performed to predict anti-Xa concentrations of observed fondaparinux regimens at various time points. The simulated concentrations were also compared with observed anti-Xa concentrations to evaluate the robustness of the final PK model.

## Results

During the study timeframe, 224 critically ill adult patients with any medical diagnosis code indicating renal impairment while receiving fondaparinux were identified. Of these, 95 were included. The most common reason for exclusion was the receipt of fondaparinux for < 72 hours (n = 103). Of the remaining patients excluded, 16 received therapeutic fondaparinux, and 10 had a CrCl > 50 mL/min.

Included patients comprised an elderly, surgical population who received an intermediate course of therapy (median = 7 days). The majority of patients (Table 1) had moderate renal impairment (n = 64; 67.4%) followed by CVVH (n = 16; 16.8%), severe renal impairment (n = 10; 10.5%), and HD (n = 5; 5.3%). In total, 35 (36.8%) patients had a contraindication to fondaparinux per the package labeling: 31 with CrCl < 30 mL/min and four with weight < 50 kg.

**Table 2.** Patient Characteristics.

| | Monitoring (n = 19) | No Monitoring (n = 76) | *P* |
|---|---|---|---|
| Male, n (%) | 10 (52.6) | 45 (59.2) | 0.27 |
| Age, years[a] | 68 (39-77) | 72.5 (20-87) | 0.03 |
| Actual weight, kg[a] | 84 (50-135) | 76 (42-144) | 0.25 |
| CrCl < 30 mL/min ± RRT, n (%) | 13 (68.4) | 18 (23.7) | 0.04 |
| Surgical service, n (%) | 13 (68.4) | 57 (75) | 0.34 |
| Regimens per patient, n[a] | 1 (1-7) | 1 (1-3) | 0.63 |
| DDD, mg[a,b] | 2.5 (0.6-2.5) | 2.5 (1.25-2.5) | |
| Duration, days[a] | 6 (3-128) | 8 (3-61) | 0.05 |
| Dosing frequency, n (%) | | | |
| Every 24 hours | 19 (65.5) | 78 (91.8) | |
| Every 48 hours | 9 (31) | 6 (7.1) | |
| Every 72 hours | 0 (0) | 1 (1.2) | |
| Posthemodialysis | 1 (3.5) | 0 (0) | |
| ICU LOS, days[a] | 20 (2-103) | 18.5 (1-96) | 0.44 |
| Hospital LOS, days[a] | 38 (7-148) | 25 (8-136) | 0.22 |
| Hematology consult, n (%) | 18 (94.7) | 20 (26.3) | <0.001 |
| HIT suspected, n (%) | 16 (84.2) | 48 (63.2) | 0.1 |
| HIT confirmed, n (%) | 3 (15.8) | 0 (0) | 0.21 |
| Clinically significant bleeding, n (%) | 0 (0) | 4 (5.3) | 0.58 |
| Incidence of new VTE prior to fondaparinux, n (%) | 2 (10.5) | 2 (2.6) | 0.18 |

Abbreviations: CrCl, creatinine clearance; DDD, defined daily dose; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; LOS, length of stay; RRT, renal replacement therapy; VTE, venous thromboembolism.
[a]Median (range).
[b]Fondaparinux prescribed dose: 2.5 or 1.25 mg.

The most common reason for fondaparinux administration was suspected HIT (n = 64, 67.4%). The remaining 31 patients received fondaparinux because of physician discretion (n = 29) or persistent thrombocytopenia (n = 2). Three cases of confirmed HIT were identified, and all occurred prior to fondaparinux initiation. A total of 38 (40%) patients were billed for a hematology consult during their targeted admission. Most consults (n = 33; 86.8%) were for suspected HIT (Table 2).

## *Dosing and Monitoring*

In the 95 patients included, 114 dosing strategies were observed. The median defined daily dose was lowest in patients receiving HD (0.9 mg), followed by CVVH (1.9 mg), severe renal impairment (2.5 mg), and moderate renal impairment (2.5 mg). A dosing frequency other than every 24 hours was more common in patients with severe renal impairment or those receiving RRT.

Overall, 19 (20%) patients received anti-Xa monitoring (Table 2). Hematology consults, severe renal impairment or RRT, and dosing intervals other than every 24 hours were more common in patients who received monitoring. These patients were also younger, with shorter durations of therapy. Of the 49 concentrations obtained, 29 (59.2%) were drawn three to five hours post-dose. In all, 13 (41.9%) patients with severe renal impairment or renal failure requiring RRT had at least one appropriately timed peak anti-Xa level drawn three to five hours post-dose (Table 1). Appropriately timed peak anti-Xa concentrations were more common in patients with severe renal impairment or RRT compared with those with moderate renal impairment.

## *Bleeding and Thrombosis*

ICD-9 coding identified 31 patients with bleeding. On chart review, four patients (4.2%) met our criteria for clinically significant bleeding. Two of these patients had a CrCl of 30 to 50 mL/min. The remaining two patients were receiving RRT. Bleeding events included gastrointestinal bleeding (n = 2), bronchial artery hemorrhage (n = 1), and hemoptysis (n = 1). Transfusion requirements within 48 hours of the four bleeding events ranged from two to five units of packed red blood cells. The duration of fondaparinux therapy prior to an event was variable (median = 8 days). Patient weight ranged from 65 to 105 kg. Anti-Xa serum concentration monitoring was not performed in any patient who experienced a clinically significant bleed. Of the four patients, two were admitted to surgical services. Neither event appeared to be related to a surgical procedure.

In all, 11 patients were identified as having a VTE based on ICD-9 coding. After chart review, four events met our definition of VTE (Table 2). Events comprised one

lower- and three upper-extremity VTEs. All VTEs identified occurred prior to fondaparinux initiation.

### PK Analysis

Because of the limited number of observed anti-Xa concentrations, a population PK analysis using a nonlinear mixed-effects model was conducted to aid in interpretation of available concentrations. Of the models tested, a two-compartment model with first-order absorption and linear elimination best described the PK of anti-Xa. The parameter estimates for the final model are presented in Figure 1A. Among the estimated PK parameters, IIV was assigned on $K_a$, CL, Vc, and Vp. As shown in Figure 1A, the standard error of the estimated parameters, IIV and RV, were within reasonable ranges. Secondary to the limited number of observed anti-Xa plasma concentrations available, $K_a$ was extracted from the literature.[20] Because fondaparinux is primarily eliminated via the kidneys, CrCl was tested as a covariate to evaluate its relationship with anti-Xa clearance; however, a significant relationship was not observed. The remaining PK parameters were estimated. Our values are consistent with those in previous literature.[20]

The goodness-of-fit plot describing the final model is presented in Figure 1B. Individual-predicted anti-Xa concentrations versus the observed concentrations were symmetrically distributed around the line of identity without bias, thus indicating that our final PK model adequately described anti-Xa PK. After model fitting, model simulation using PK parameters obtained from the final model was conducted (Figure 2). Predicted concentrations were consistent with the observed values, further validating the strength of our PK model.

Predicted anti-Xa levels for patients who had a level drawn at any time point are presented in Figure 2. For all renal impairment cohorts, peak anti-Xa levels above the upper limit of our prophylactic range (0.39-0.5 μg/mL) were observed in at least one patient within the first week of therapy. This also occurred in patients who received empirically dose-reduced regimens. Significant intrapatient variability was predicted even in patients who received the same dosing regimen.

## Discussion

A variety of fondaparinux dosing and monitoring strategies have been described in patients with moderate and severe renal impairment.[4,5,7-11,19-24] Safety data surrounding the use of fondaparinux in these patients is lacking. This lack of consistency was reflected in the variable prescribing practices that we observed in our institution over the six-year study period.

Previous data have indicated that patients with moderate renal impairment receiving fondaparinux 2.5 mg daily may need empirical dose reductions secondary to drug accumulation, leading to an increased risk of bleeding.[21,22] Recently, prophylactic fondaparinux dosing strategies in patients with CrCl = 20 to 50 mL/min have been investigated.[20-23] Turpie et al[21] observed similar pharmacokinetic profiles when comparing patients with CrCl = 20-50 mL/min who received fondaparinux 1.5 mg daily with healthy volunteers receiving 2.5 mg daily. When studied in a surgical population, major bleeding rates were comparable for those with moderate renal impairment receiving fondaparinux 1.5 mg daily and those with normal renal function receiving low-molecular-weight heparin or oral direct thrombin inhibitors.[22] This practice has been adopted outside of the United States because the European Agency for the Evaluation of Medicinal Products recommends reduced-dose fondaparinux for the prevention of VTE in moderate renal impairment.[24]

In our investigation, empirical dose reductions in patients with moderate renal impairment occurred less frequently than in those with severe renal impairment or patients receiving RRT. This is likely reflective of the lack of specific guidance surrounding dose reductions for patients with moderate renal impairment. Based on our PK simulation, it is likely that a number of patients in our moderate renal impairment cohort, who received standard-dose prophylactic fondaparinux, experienced supratherapeutic levels during therapy.

In our cohort of patients with severe renal impairment and those receiving RRT, empirical dose adjustments occurred more frequently, and anti-Xa monitoring was more common. This difference in practice may be reflective of a heightened awareness of bleeding risk. Whereas many of the anti-Xa levels drawn were subtherapeutic, few of the levels were peaks and are, therefore, difficult to interpret. Our PK simulation demonstrated intrapatient variability, particularly in the cohort of patients receiving CVVH who had the greatest number of data points available for analysis.

Decreased CrCl is an independent predictor of major bleeding in those receiving fondaparinux versus low-molecular-weight heparin or placebo.[4] Anti-Xa monitoring may be used to identify drug accumulation in patients with renal impairment; however, there is nothing in the literature to suggest a correlation between anti-Xa serum concentration and bleeding or thrombosis. We observed four (4.2%) clinically significant bleeding events in patients with moderate renal impairment and those receiving RRT. None of these patients received anti-Xa monitoring. This event rate is similar to that in previous literature that included patients with moderate to severe renal dysfunction and suggests that empirical dose modification, or anti-Xa-guided dose modification, may be warranted in this population.[5,15-26]

Our study has several noteworthy limitations, including the use of medical diagnosis codes to identify clinically significant bleeding and thromboembolic events. This method has been utilized in other retrospective analyses evaluating

A

| PK Parameters | Estimate (CV%) | IIV and RV | Value |
|---|---|---|---|
| Ka (1/hr) | 1.36 fix | $\Omega_{ka}^2$ | 0.156 |
| Vc (L) | 12.0 (16) | $\Omega_{Vc}^2$ | 0.488 |
| Vp (L) | 5.42 (122) | $\Omega_{Vp}^2$ | 3.53 |
| CL (L/hr) | 0.169 (15) | $\Omega_{CL}^2$ | 0.296 |
| Q (L/hr) | 0.0501 (42) | | |
| Lag time (hr) | 1.19 (63) | $\sigma^2$ | 0.222 |

B

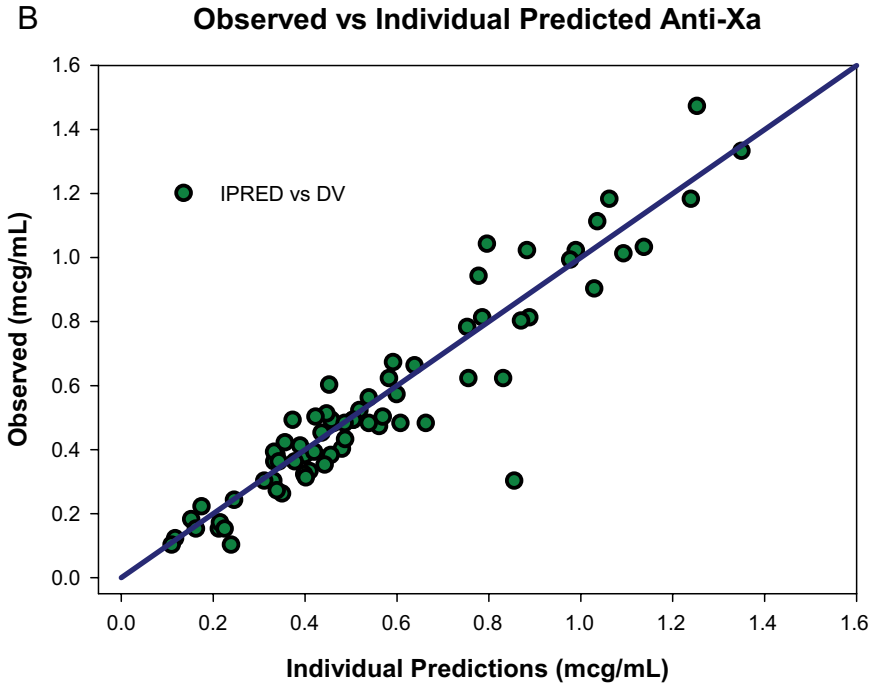


**Figure 1.** A. Estimated anti-Xa pharmacokinetic (PK) parameters. B. Anti-Xa pharmacokinetic model goodness-of-fit plot: observed (DV) versus individual-predicted (IPRED) anti-Xa plasma concentrations.
Abbreviations: CL, apparent clearance; CV, coefficient of variance; IIV, interindividual variability; Ka, absorption rate constant; Q, intercompartmental clearance; RV, residual variability; Vc, apparent central volume; Vp, apparent peripheral volume.

the safety and efficacy of anticoagulation.[13] Although manually reviewing identified events for accuracy against bleeding definitions utilized in other prospective investigations strengthens the validity of our findings, opportunity exists for underreporting. Second, an adjusted body weight was used when calculating CrCl via the Cockcroft and Gault equation for patients whose weight was greater than their IBW. Data suggest the use of actual body weight when calculating CrCl via the Cockcroft and Gault equation for patients of normal weight; however, we surmised that the difference in calculated CrCl would not affect categorization into our predefined renal categories.[12] The small study

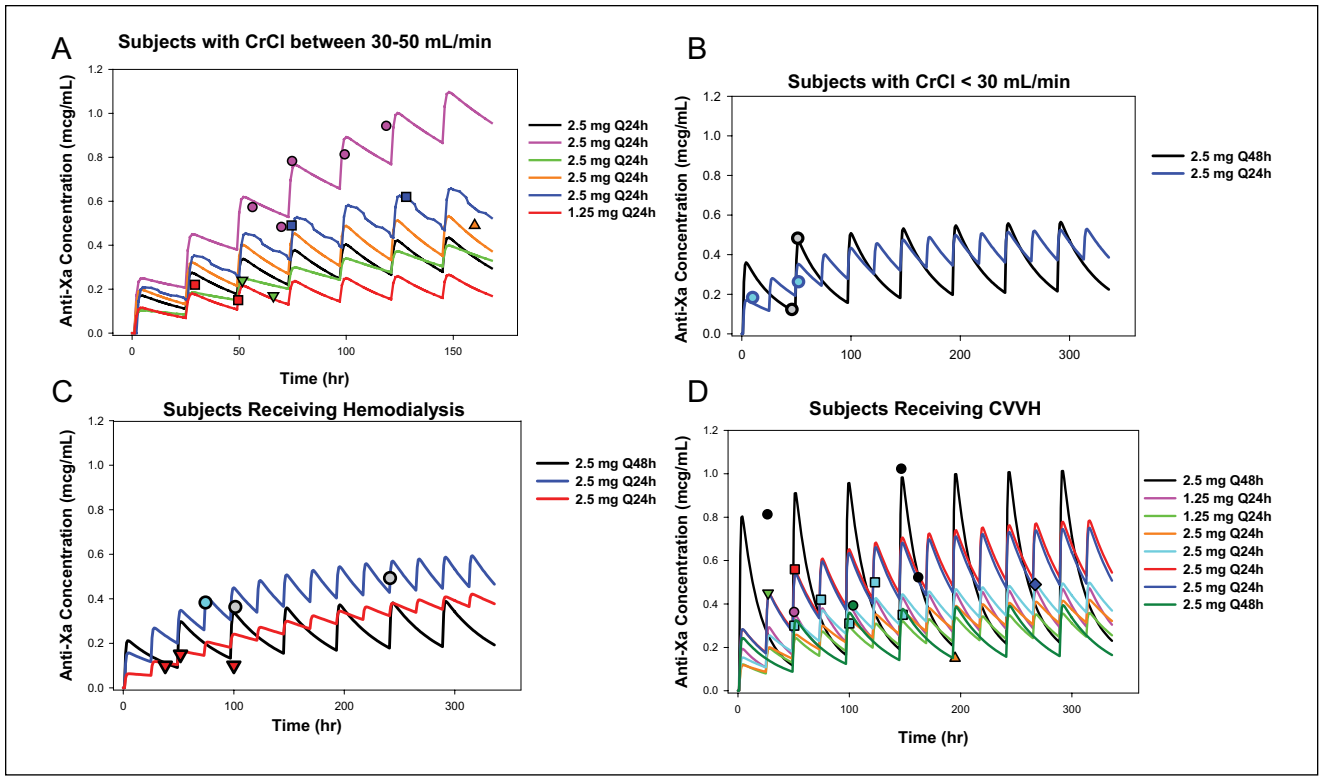


**Figure 2.** Pharmacokinetic model predicted and observed anti-Xa concentrations in (A) participants with CrCl = 30-50 mL/min; (B) participants with a CrCl < 30 mL/min; (C) participants receiving hemodialysis; and (D) participants receiving CVVH. Lines represent predicted concentrations and symbols represent observed concentrations.
Abbreviations: CrCl, creatinine clearance; CVVH, continuous venovenous hemofiltration.

sample size was also a limiting factor. Over the six-year study timeframe, we observed infrequent use and monitoring of fondaparinux in patients with moderate to severe renal impairment and renal failure, including RRT. The limited number of observed anti-Xa concentrations also likely affected our ability to detect a covariate effect with CrCl in our population PK model. Of note, previous work has shown a significant covariate effect with CrCl and anti-Xa clearance.[19] This also impaired our ability to identify distinct prescribing patterns and trends.

## Conclusions

A variety of dosing and monitoring strategies were observed at our institution in critically ill patients with moderate and severe renal impairment receiving fondaparinux for VTE prophylaxis. Empirical dose reductions and anti-Xa monitoring were more common in patients with severe renal impairment or RRT than in patients with moderate renal impairment, although little consistency was noted. Our PK simulations indicate that dose reductions and therapeutic drug monitoring are warranted in both patients with moderate and severe renal impairment, including those receiving RRT. As a result of the increased risk of bleeding observed in patients with a CrCl ≤ 50 mL/min and the degree of variability in existing prescribing practices, we suggest the development of a fondaparinux dose reduction protocol, including routine peak anti-Xa serum concentration monitoring in patients with a CrCl ≤ 50 mL/min, with consideration placed on restricting the use of fondaparinux in patients with a CrCl < 30 mL/min to approval by a clinical pharmacy specialist or a board-certified hematology specialist at centers with high-volume fondaparinux use.

Additional data are warranted to determine an appropriate defined daily dose for patients with a CrCl between 30 and 50 mL/min, CrCl < 30 mL/min, and patients receiving HD or CVVH.

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### Authors' Note

Information about presentation of the work as an abstract or poster: Portions of the included data were presented in abstract form: Use of fondaparinux for venous thromboembolism prophylaxis in critically ill adult patients with moderate renal insufficiency: *Blood*. 2013;122(21). The remaining data were presented

in abstract and poster form at the 43rd Critical Care Congress of the Society of Critical Care Medicine in January 2014, San Francisco, CA, "Fondaparinux use in severe renal impairment and renal failure requiring renal replacement therapy": *Crit Care Med*. 2013;41(12).

## Declaration of Conflicting Interests

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## References

1. Uchino S, Kelleum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294:813-818.
2. Monreal M, Falga C, Valle R, et al. Venous thromboembolism in patients with renal insufficiency: findings from the REITE registry. *Am J Med*. 2006;119:1073-1079.
3. Donat F, Duret JP, Santoni A, et al. The pharmacokinetics of fondaparinux sodium in healthy volunteers. *Clin Pharmacokinet*. 2002;41(suppl 2):1-9.
4. Eikelboom JW, Quilan DJ, O'Donnell M. Major bleeding, mortality, and efficacy of fondaparinux in venous thromboembolism prevention trials. *Circulation*. 2009;120:2006-2011.
5. Arixtra (fondaparinux) injection [product information]. Research Triangle Park, NC: GlaxoSmithKline; 2011.
6. Garcia DA, Baglin TP, Weitz JI, Samama MM; American College of Chest Physicians. Parenteral anticoagulants: antithrombotic therapy and prevention of thrombosis. *Chest*. 2012;141(suppl 2):S24-S43.
7. Mahieu E, Claes K, Jacquemin M, et al. Anticoagulation with fondaparinux for hemodiafiltration in patients with heparin-induced thrombocytopenia: dose-finding study and safety evaluation. *Artif Organs*. 2013;37:482-494.
8. Wahby K, Jerusalem Z, Lazar S, Gojka M, Tennenberg SD. Extended interval fondaparinux interval fondparinux dosing for DVT prophylaxis in critically ill patients with renal failure. *Crit Care Med*. 2012;40:1-328. doi:10.1097/01.ccm.0000424339.48131.6e.
9. Haase M, Bellomo R, Rocktaeschel J, et al. Use of fondaparinux (ARIXTRA) in a dialysis patient with symptomatic heparin-induced thrombocytopenia type II. *Nephrol Dial Transplant*. 2005;20:444-446.
10. Kalicki RM, Aregger F, Lammle B, Frey FJ, Uehlinger DE. Use of the pentasaccharide fondaparinux as an anticoagulant during hemodialysis. *Thromb Haemost*. 2007;98:1200-1207.
11. Brown P, Jay R, Fox A, Oliver M. Chronic fondaparinux use in a hemodialysis patient with heparin-induced thrombocytopenia type II and extracorporeal circuit thrombosis: a case report and review of the literature. *Hemodial Int*. 2013;17:444-449.
12. Winter MA, Guhr KN, Berg GM. Impact of various body weights and serum creatinine concentrations on the bias and accuracy of the Cockcroft-Gault equation. *Pharmacotherapy*. 2012;32:604-612.
13. Arnason T, Wells PS, Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res*. 2006;118:253-262.
14. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692-694.
15. Agnelli G, Bergqvist D, Cohen AT, Gallus AS, Gent M; PEGASUS investigators. Randomized clinical trial of postoperative fondaparinux versus perioperative dalteparin for prevention of venous thromboembolism in high-risk abdominal surgery. *Br J Surg*. 2005;92:1212-1220.
16. Bauer K, Eriksson BI, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Major Knee Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery. *N Engl J Med*. 2001;345:1305-1310.
17. Eriksson BI, Lassen MR; PENTasaccharide in Hip-FRActure Surgery Plus Investigators. Duration of prophylaxis against venous thromboembolism with fondaparinux after hip fracture surgery. *Arch Intern Med*. 2003;163:1337-1342.
18. Lassen MR, Bauer KA, Eriksson BI, Turpie AG; European Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: a randomized double-blind comparison. *Lancet*. 2002;359:1715-1720.
19. Hester W, Fry C, Gonzalez D, Cohen-Wolkowiez M, Inman BA, Ortel TL. Thromboprophylaxis with fondaparinux in high-risk postoperative patients with renal insufficiency. *Thromb Res*. 2014;133:629-633.
20. Delavenne X, Zufferey P, Nguyen P, et al. Pharmacokinetics of fondaparinux 1.5 mg once daily in a real-world cohort of patients with renal impairment undergoing major orthopaedic surgery. *Eur J Clin Pharmacol*. 2012;68:1403-1410.
21. Turpie AG, Lensing AW, Fuji T, Boyle DA. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. *Blood Coagul Fibrinolysis*. 2009;20:114-121.
22. Mismetti P, Samama CM, Rosencher N. Venous thromboembolism prevention with fondaparinux 1.5 mg in renally impaired patients undergoing major orthopaedic surgery. *Thromb Haemost*. 2012;107:1151-1160.
23. Ageno W, Riva N, Noris P, et al. Safety and efficacy of low-dose fondaparinux (1.5 mg) for the prevention of venous thromboembolism in acutely ill medical patients with renal impairment: the FONDAIR study. *J Thromb Haemost*. 2012;10:2291-2297.
24. GlaxoSmithKline receives EU approval for a new therapeutic indication for Arixtra (fondaparinux). http://www.gsk.com/en-gb/search/?q=Fondaparinux+European+Approval#. Accessed June 5, 2014.
25. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med*. 2003;349:1695-1702.
26. Buller HR, Davidson BL, Decousus H, et al. Fondaparinux or enoxaparin for the initial treatment of deep venous thromboembolism. *Ann Intern Med*. 2004;140:867-873.