Outcomes and Practice Patterns Study. *Nephrol Dial Transplant*. 2008;23:3219-3226.

5. Lynch JR, Wasse H, Armistead NC, McClellan WM. Achieving the goal of the Fistula First Breakthrough Initiative for prevalent maintenance hemodialysis patients. *Am J Kidney Dis*. 2011;57:78-89.

6. Tangri N, Moorthi R, Tighiouhart H, Meyer KB, Miskulin DC. Variation in fistula use across dialysis facilities: is it explained by case-mix? *Clin J Am Soc Nephrol*. 2010;5:307-313.

7. VanLare JM, Conway PH. Value-based purchasing—national programs to move from volume to value. *N Engl J Med*. 2012;367:292-295.

8. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Medicare Program; End-Stage Renal Disease Prospective Payment System and Quality Incentive Program; Ambulance Fee Schedule; Durable Medical Equipment; and Competitive Acquisition of Certain Durable Medical Equipment, Prosthetics, Orthotics and Supplies. http://gpo.gov/fdsys/pkg/FR-2011-11-10/pdf/2011-28606.pdf. Accessed March 4, 2012.

9. Department of Health and Human Services, Centers for Medicare & Medicaid Services. Final Draft ESRD Statement of Work 2-3-2012. https://www.fbo.gov/utils/view?id=3091b1a8cb6d12c223633cc23047dae6. Accessed March 4, 2012.

10. Wish JB. Vascular access for dialysis in the United States: progress, hurdles, controversies and the future. *Semin Dial*. 2010; 23:614-618.

Received May 13, 2012. Accepted in revised form September 10, 2012. Originally published online November 16, 2012.

Because a quorum could not be reached after those editors with potential conflicts recused themselves from consideration of this manuscript, the peer-review and decision-making processes were handled entirely by an Associate Editor (Arif Asif, MD) who served as Acting Editor-in-Chief. Details of the journal's procedures for potential editor conflicts are given in the Editorial Policies section of the AJKD *website.*

http://dx.doi.org/10.1053/j.ajkd.2012.09.014

Use of Fondaparinux for Circuit Patency in Hemodialysis Patients

To the Editor:

Unfractionated heparin is generally the preferred anticoagulant in hemodialysis (HD) patients due to its predominantly reticular endothelial elimination and lack of accumulation in kidney failure.[1] Heparin-exposed patients are at higher risk of developing heparin-induced thrombocytopenia (HIT),[2] and choices for anticoagulation in this patient population are limited. Direct thrombin inhibitors such as argatroban, lepirudin, and bivalirudin are expensive and require intravenous administration.[3,4] The factor Xa inhibitor danaparoid can be given subcutaneously, but availability is limited in some countries. Fondaparinux is a synthetic factor Xa–selective pentasaccharide that, unlike heparin, has very little effect on platelet aggregation.[3] It currently is contraindicated in patients with severely decreased kidney function (creatinine clearance <30 mL/min) due to its almost complete renal elimination.[5] However, as a once-daily cost-effective prefilled syringe, it is an attractive alternative in outpatient HD patients.

On this basis, we reviewed the literature available and established internal guidelines for fondaparinux use in our HD patients intolerant to heparin (either because of HIT or anaphylactoid-type reactions). These guidelines were reviewed by a number of experts in nephrology, hematology, and pharmacy. We suggested that fondaparinux, 2.5 mg, be given subcutaneously pre-HD for circuit patency, with anti-Xa levels measured before the fourth dose when initiating therapy and weekly thereafter. Adherence to these suggestions were at the discretion of the physicians providing care. Between January and May 2011, three patients receiving HD thrice weekly and using fondaparinux for circuit patency were identified (Table 1). All patients received fondaparinux, 2.5 mg, pre-HD for the duration of therapy. Our main objectives were to assess for accumulation by measuring anti-Xa levels and to monitor for clinical treatment failure (intradialytic circuit clotting) and side effects. Two sets of anti-Xa levels (pre- and post-HD) were drawn 1 week apart for each patient (Table 2). One pre-HD level was excluded from the analysis because it was drawn postdose and resulted in a much higher level than expected. The average pre-HD level was 0.17 (range, 0.11-0.25) μg/mL. Post-HD levels ranged from 0.34-0.64, with a mean level of 0.51 μg/mL. None of the patients experienced bleeding or other side effects associated with the drug. Intradialytic circuit clotting was observed in one patient after initiation of the third HD session and required catheter flushing with alteplase. However, with continued use, no further clotting was observed in that or any other patient.

No literature exists to support targeting anti-Xa levels for maintaining circuit patency in HD patients. Instead, these levels were drawn to assess for accumulation. The levels obtained essentially approximated the ranges recommended for prophylaxis (0.2-0.4 μg/mL), which we inferred as being suitable anti-Xa inhibition

Table 1. Patient Characteristics

	Patient 1	Patient 2	Patient 3
Age (y)/sex	76/F	80/F	59/M
Height (cm)	157	156	163
Weight (kg)	49	79	65
CKD cause	Unknown	Type 1 diabetes	Type 2 diabetes
HD vintage (mo)	180	4	12
Duration of HD session (h)	3.5	4	4
Dialyzer type	Xenium 190[a]	Xenium 190[a]	Optiflux 200[b]
Mean blood flow rate (mL/min)	350	360	340
Mean dialysis flow rate (mL/min)	500	500	750
Fondaparinux indication	Circuit patency (HIT)	Circuit patency (anaphylactoid reaction)	Circuit patency (HIT)

Abbreviations: CKD, chronic kidney disease; HD, hemodialysis; HIT, heparin-induced thrombocytopenia.
[a]Polynephron polyethersulfone (Baxter Healthcare Corp).
[b]Advanced Fresenius polysulfone membrane (Fresenius Medical Care).

Table 2. Anti-Xa Levels

Patient	Anti-Xa levels (μg/mL)		Dose No.
	Pre-HD	Post-HD	
1	—	0.48	1
	0.19	0.64	4
2	0.25	0.57	123
	0.14	0.34	126
3	0.73[a]	0.53	30
	0.11	0.48	33

Note: All patients received fondaparinux, 2.5 mg, subcutaneously pre-HD. Anti-Xa levels were measured by a colorimetric assay (Biophen Arixtra Control Kit, HYPHEN BioMed) that reports anti-Xa levels in μg/mL, which is equivalent to IU/mL.

Abbreviation: HD, hemodialysis.

[a]Level drawn postdose, excluded from analysis.

for circuit patency. Pre-HD levels obtained before the fondaparinux dose represented true trough levels in this patient population and were used as markers for accumulation. The patient who received 126 doses of fondaparinux had pre-HD anti-Xa levels of 0.25 and 0.14 μg/mL at doses 123 and 126, respectively, providing encouragement that long-term use of fondaparinux, 2.5 mg, pre-HD does not cause significant accumulation.

Clinically, fondaparinux was effective for maintaining HD circuit patency in our patients. Although one patient experienced an episode of complete circuit clotting, we hypothesize that the third dose may have been too soon to evaluate its effectiveness. With continued use, there were no further episodes. Fondaparinux was very well tolerated, with no bleeding or other side effects noted. All 3 patients received a different number of fondaparinux doses, increasing our confidence with initiating, maintaining, and using the medication long term. There was no apparent association between higher pre- or post-HD anti-Xa levels and the number of fondaparinux doses, implying that minimal accumulation occurred with long-term treatment during HD.

Literature on the use of fondaparinux in HD is limited. Preliminary cohort data suggested that fondaparinux use in high-flux polysulfone dialyzers increased the risk of extracorporeal circuit and dialyzer thrombosis.[6] However, 3 case reports[7-9] described successful use of fondaparinux in high-flux dialyzers with varying dosing regimens and treatment durations. Our study also showed similar success. In addition, we were able to demonstrate efficacy with minimal accumulation or clinical side effects at various durations of treatment and over extensive repeated administration.

The limited number of patients in this study limits the generalizability of these findings. However, this research suggests that through quantitative anti-Xa monitoring and clinical correlation, fondaparinux may be a safe and effective therapeutic option for patients who are unable to receive heparin. Continued research and experience with using fondaparinux for circuit patency and other anticoagulation indications will continue to strengthen our confidence in using this drug in this patient population.

Grace Ho, BScPhm,[1] Kori Leblanc, PharmD,[1,2]
Rita Selby, MD,[1,2,3] Robert Richardson, MD,[1,2]
Michelle Hladunewich, MD,[2,3] Marisa Battistella, PharmD[1,2]
[1]University Health Network, Toronto, Canada
[2]University of Toronto, Toronto, Canada
[3]Sunnybrook Health Sciences Centre, Toronto, Canada
Corresponding author: gracewyho@gmail.com

Acknowledgements

We thank Bill Brien, MD, and Jin Huh, BScPhm, for expert review of guidelines, and Jenny Ng, BScPhm, for contributing data.

Support: None; all resources used were part of routine clinical care.

Financial Disclosure: The authors declare that they have no relevant financial interests.

References

1. Arapelle GM, Ortel TL. Heparin induced thrombocytopenia. *Annu Rev Med*. 2010;61:77-90.
2. Syed S, Reilly R. Heparin-induced thrombocytopenia: a renal perspective. *Nat Rev Nephrol*. 2009;5(9):501-511.
3. Warkentin T, Greinacher A, Koster A. Treatment and prevention of heparin induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133(suppl 6):340S-380S.
4. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2008;133(suppl 6):141S-159S.
5. GlaxoSmithKline. Arixtra Product Monograph. Mississauga, ON: GlaxoSmithKline; 2009.
6. Sombolos KI, Fragia TK, Gionanlis LC, et al. Use of fondaparinux as an anticoagulant during hemodialysis: a preliminary study. *Int J Clin Pharmacol Ther*. 2008;46(4):198-203.
7. Haase M, Bellomo R, Rocktaeschel J, et al. Use of fondaparinux (ARIXTRA) in a dialysis patient with symptomatic heparin-induced thrombocytopaenia type II. *Nephrol Dial Transplant*. 2005;20(2):444-446.
8. Wellborn-Kim JJ, Mitchell GA, Terneus WF Jr, et al. Fondaparinux therapy in a hemodialysis patient with heparin-induced thrombocytopenia type II. *Am J Health Syst Pharm*. 2010;67(13):1075-1079.
9. Solack Y, Demircioglu S, Polat I, et al. Heparin-induced thrombocytopenia in a hemodialysis patient treated with fondaparinux: nephrologists between two fires [published online ahead of print May 28, 2012]. *Hemodial Int*. http://dx.doi.org/10.1111/j.1542-4758.2012.00710.x.

Received May 31, 2012. Accepted in revised form September 25, 2012. Originally published online November 16, 2012.

http://dx.doi.org/10.1053/j.ajkd.2012.09.015