Safety and Efficacy of Fondaparinux in Renal Impairment

Journal of Pharmacy Technology
2015, Vol. 31(4) 161–166
© The Author(s) 2015
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122514567316
pharmatech.sagepub.com

Mohammad H. Al-Shaer, PharmD, BCPS¹, and Tarek Ibrahim, MCLinPharm¹

Abstract

Objective: To evaluate the cumulative evidence regarding the efficacy and safety of using fondaparinux in renal impairment, manifested by preventing new or recurrent thrombosis and the incidence of bleeding, respectively. **Data Sources:** We searched the MEDLINE and Cochrane databases for relevant studies from 1966 until November 2014, using the terms “fondaparinux” and “renal failure” or “dialysis.” Additional references were identified from review of literature citations. **Study Selection and Data Extraction:** Inclusion criteria were articles in English language and patients with creatinine clearance (CrCl) less than 50 mL/min. Exclusion criteria were using fondaparinux as an anticoagulant for dialyzer circuit patency, abstracts, case reports, case series, pediatrics (<18 years), and pharmacokinetic studies with no clinical efficacy and safety results. **Data Synthesis:** Our search retrieved 4 cohort studies, 1 clinical trial, and 1 randomized clinical trial (RCT) subgroup analysis. A total of 3237 patients received fondaparinux with a dose ranging from 1.25 mg to 2.5 mg daily. Three studies investigated fondaparinux as a prophylactic agent, 2 as a treatment agent, and 1 study investigated both. The only study with control group was the RCT subgroup analysis, which compared fondaparinux to enoxaparin. A total of 470 patients developed thromboembolic complications or death and 169 developed major bleeding. The composite outcome of safety and efficacy in the RCT subgroup analysis was significantly lower in fondaparinux group compared with the enoxaparin group ($P = .001$). **Conclusions:** Current evidence regarding the safety and efficacy of fondaparinux in renally impaired patients is limited and does not support its use in such population.

Keywords

anticoagulants, renal failure, kidney failure, dialysis, anticoagulation

Background

Chronic kidney disease (CKD) is an international public health problem.¹ It is estimated that more than 20 million people within the United States have CKD of varying degrees of seriousness.² Other regions including Europe, Australia, and Asia also confirm this high prevalence of CKD.^{3–6} It is classified as mild, moderate, or severe if the glomerular filtration rate is 60 to 89, 30 to 59, or 15 to 29 mL/min/1.73 m², respectively.⁷ Patients with CKD are considered to be at high risk of developing venous thromboembolism (VTE). In one study, patients with renal impairment had a 2-fold risk of developing VTE compared with patients with normal kidney function.⁸ Additionally, this population group is known to have increased levels of inflammatory and procoagulant factors,⁹ but they are also vulnerable to bleeding risk.¹⁰ Therefore, anticoagulation in patients with renal impairment requires the balancing between the risk of thrombosis and bleeding.

Fondaparinux is a pentasaccharide that binds to anti-thrombin and inactivates factor Xa.^{11,12} Unstable angina, non-ST segment elevation myocardial infarction, ST segment

elevation myocardial infarction, and heparin-induced thrombocytopenia (HIT) are some conditions in which fondaparinux is used for prevention or treatment of VTE. The drug has a high bioavailability (~100%),¹³ with elimination half-life of 17 to 21 hours, making it easier to be administered once daily.¹² Since the drug is not metabolized and is excreted through kidneys, the fondaparinux dose needs to be adjusted in patients with renal impairment.¹³ The total clearance of fondaparinux decreases by 25%, 40%, and 55% when creatinine clearance (CrCl) is 50 to 80, 30 to 50, and <30 mL/min, respectively.¹² However, specific dosing recommendations for patients with renal impairment are lacking. The American College of Chest Physicians recommends decreasing the dose of fondaparinux by 50% when CrCl is between 30 and 50 mL/min.¹⁴ Once CrCl drops below 30 mL/min,

¹Al Wakra Hospital—Hamad Medical Corporation, Doha, Qatar

Corresponding Author:

Mohammad H. Al-Shaer, PharmD, BCPS, Department of Pharmacy, Al Wakra Hospital—Hamad Medical Corporation, Doha 82228, Qatar.
Email: malshaer1@hamad.qa

fondaparinux use is contraindicated.¹² In Europe, fondaparinux 1.5 mg once daily is approved for VTE prevention when CrCl is between 20 and 50 mL/min based on a prospective cohort study of 442 orthopedic surgical patients.^{15,16}

Since it is given once daily, needs less frequent monitoring, and relatively cheaper than other parenteral alternatives, fondaparinux is considered an attractive option that warrants further investigation. We aim to review and evaluate the cumulative evidence regarding the safety and efficacy of using fondaparinux as a prophylactic or treatment anticoagulant in patients with renal impairment.

Literature Review

The MEDLINE and Cochrane Databases were searched for relevant studies between 1966 until November 2014, using the following terms: fondaparinux, renal failure, and dialysis. Additional citations were identified from bibliographies of related articles. We included studies in English language and reported the use of fondaparinux in patients with CrCl less than 50 mL/min for the purpose of anticoagulation treatment or thromboprophylaxis. Anticoagulation for dialyzer circuit patency, abstracts, case reports, case series, studies conducted on pediatrics (less than 18 years old), and pharmacokinetic studies without clinical efficacy and safety results were excluded. The primary endpoints were the clinical efficacy and safety of the regimen manifested by preventing new or recurrent thrombosis and the incidence of bleeding, respectively. This was determined both during and after fondaparinux administration period.

Our search strategy resulted in 25 studies. From these, 6 studies—4 cohorts, 1 clinical trial, and 1 randomized clinical trial (RCT) subgroup analysis—met our criteria (Table 1). Three studies investigated fondaparinux as a prophylactic agent, 2 as a treatment agent, and 1 study investigated both indications.

Hester et al¹⁷ reported a clinical trial, partially funded by GlaxoSmithKline, on 9 surgical patients given fondaparinux for VTE prevention. All patients underwent surgical procedure for urologic malignancy, except one patient who underwent a total knee arthroplasty. Patients' creatinine clearance was calculated using Cockcroft-Gault equation. Fondaparinux dose was 1.5 mg subcutaneously (SC) daily, or the frequency interval was increased based on anti-Xa level. However, there was no mention of how long these intervals were, how many patients required them, and what their CrCl was at that time. The majority of anti-Xa trough levels were either slightly elevated or below the therapeutic range (0.2–0.7 µg/mL). One patient developed internal jugular vein thrombosis postoperatively, 24 hours after the first dose of fondaparinux. Consequently, the patient was converted to a therapeutic dose of enoxaparin. The patient had history of deep vein thrombosis (DVT) who was on warfarin prior to surgery with inferior vena cava filter placement, and had a transient episode of asymptomatic atrial

fibrillation postoperatively. Another patient had a 2 g/dL drop in hemoglobin while on fondaparinux, and received 1 unit of packed red blood cells (PRBC), with an anti-Xa level of <0.1 µg/mL. However, no patients within this study developed hemorrhagic complications. Some of the limitations of this study were not having a control group, the sample size was small, and patients were followed during their hospital stay only, with mean duration of 8.2 days (range = 5–13 days). Additionally, patients taking aspirin, clopidogrel, or nonsteroidal anti-inflammatory drugs (NSAIDs) were excluded that might have provided safety data regarding using fondaparinux along with these medications.

FONDAIR¹⁸ was a cohort study that followed 206 acutely ill medical patients prospectively. Subjects were initiated on fondaparinux 1.5 mg SC daily for the prevention of VTE, and the median hospital stay was 11 days (range = 2–58). Two thirds of patients were on concurrent antiplatelet therapy (62.1%), 4.4% on NSAIDs, and 2.9% had history of previous major bleeding. The mean Charlson comorbidity index was 8.2 ± 1.5 , and only 1 patient had a score below 5, which means that most patients are at high risk of death. Patients had renal impairment based on the calculated CrCl (20–50 mL/min) using Modification of Diet in Renal Disease (MDRD) formula, with 37.2% having CrCl below 30 mL/min. Investigators followed the patients for 1 month after hospital discharge. Primary endpoint was the incidence of major bleeding during and 2 days after therapy. The secondary endpoints were the incidence of nonmajor bleeding during and 2 days after therapy as well as the symptomatic VTE during treatment. One patient (0.49%) developed major gastrointestinal (GI) bleed that required blood transfusion. An additional patient treated with fondaparinux for 14 days had a major bleeding during the follow-up period and was readmitted 5 days after hospital discharge with pneumonia and severe anemia and found to have duodenal ulcers. On the other hand, 8 nonmajor bleeding events (3.88%) were due to macroscopic hematuria after catheterization ($n = 4$), rectal bleeding with internal hemorrhoid ($n = 1$), oral bleeding with tongue varices ($n = 1$), epistaxis ($n = 1$), and GI bleeding ($n = 1$). As a result, a total of 9 patients developed both major and nonmajor bleeding, and when their baseline characteristics (eg, mean age in years, CrCl <30 mL/min, previous major bleeding, and concomitant antiplatelet therapy) were compared with those without bleeding events, none was found significantly associated with bleeding. Three nonfatal pulmonary embolism (PE) events (1.46%) were identified; one of them was diagnosed after single dose of fondaparinux in a patient with chronic obstructive pulmonary disease (COPD). Twenty-three patients (11.17%) died during the study period; only one event was suspected to be due to PE, though alternative diagnosis of fatal arrhythmia was also present. In this study, recruitment was stopped before the target sample size of 300 patients was reached due to slow

Table 1. Studies That Discussed Fondaparinux Use in Renal Impairment.

Study, Year	Design	Indication	Patients (n)	Renal Function (mL/min)	Age (years)	Weight (kg)	Dose (mg/day)	Anti-Xa Level	Duration (days)	Efficacy and Safety
Hester et al (2014) ¹⁷	Clinical trial	Prophylaxis for abdominal or orthopedic surgery	9	44.4 (29.5-54.6) ^a	76 (52-86) ^a	69 (53-97) ^a	1.5	Peak ^b : 0.25 µg/mL (<0.1-0.45) ^a Mid ^c : 0.16 µg/mL (0.1-0.64) ^a Trough ^b : 0.1 µg/mL (<0.1-0.22) ^a	5 (2-12) ^c	No hemorrhagic complications One patient had Hb drop by 2 g/dL One patient had suspected PE
Agono et al (2012) ¹⁸	Prospective, cohort	Prophylaxis in acutely ill medical patients	206	33 (±8.2) ^{d,e}	82 (mean)	72.3 (±16.1) ^{d,f}	1.5	NR	9.2 (±3.6) ^d	One major bleeding event Eight nonmajor bleeding events Three PE events Twenty-three deaths (one suspected to be due to PE)
Wester et al (2007) ¹⁹	Retrospective, cohort	HIT	5	16.5 (0-45) ^{a,g}	66.8 ± 12.9 ^d	NR	2.5 (n = 4), 1.25 (n = 1)	Min: 0.2 IU/mL (0-0.6) ^a Max: 0.6 IU/mL (0-0.6) ^a	1.8 to 6.5	Two minor bleeding events during fondaparinux therapy period
Fox et al (2007) ²⁰	RCT subgroup analysis	Non-STE ACS	514 ^h	<58 ^e	72.4 ± 8.9 ^d	NR	2.5	NR	5.2 (2-8) ^a	Death, MI, refractory ischemia: Day 9: 6.7%, day 30: 10%, day 180: 17.9% Major bleed: Day 9: 2.8%, day 30: 4.2%, day 180: 5.8% Day 10: major bleed 4.5%, clinical bleed 0.5%, VTE 0.5% Day 30: major bleed 5.2%, clinical bleed 0.7%, VTE 0.7%, mortality 2.3% Two bleeding events (one was fatal) Two thrombotic events
Mismetti et al (2012) ¹⁶	Prospective, cohort	Prophylaxis in orthopedic surgery	442	39 (±8) ^d	81.4 (±6.6) ^f	62.1 (±12.4) ^d	1.5	NR	16 (±12.5) ^d	
Cegarra-Sanmartin et al (2014) ²¹	Retrospective, cohort	HIT	14	45 (n = 2), CVVHDF (n = 11), HD (n = 1)	64 (30-77) ^c	NR	2.5 (n = 10), 3 (n = 1), 1.5 (n = 2), 1.25 (n = 1)	Max: 0.92 (0.58-1.85) ^a Min: 0.21 (0.02-1.25) ^a	8 to 35	

Abbreviations: CVVHDF, continuous venovenous hemodiafiltration; Hb, hemoglobin; HD, hemodialysis; HIT, heparin-induced thrombocytopenia; Max, maximum; Min, minimum; non-STE ACS, non-ST elevation acute coronary syndrome; NR, not reported; PE, pulmonary embolism; RCT, randomized controlled trial; VTE, venous thromboembolism.

^aMedian (range).
^bPeak level: 2-6 hours after dose, mid-point level: 12 ± 4 hours after dose, trough level: 1-4 hours before next dose.

^cMean (range).

^dMean ± standard deviation.

^eCalculated using Modification of Diet in Renal Disease (MDRD) formula.

^fWeight was available in 164 patients.

^gFormula used to estimate creatinine clearance was the following: urine creatinine (mmol/L) × urine volume (mL) ÷ serum creatinine (µmol/L) × urine collection time (minutes).

^hCombined number of patients on enoxaparin and fondaparinux.

enrollment. Additionally, the study lacked a control group to compare it with the fondaparinux arm. The study did include patients using antiplatelet medications, which might be more representative of the elderly population. This study was supported by a grant by GlaxoSmithKline.

Wester et al¹⁹ evaluated fondaparinux use in a retrospective, cohort study on 7 critically ill patients with suspected HIT. Only 5 patients had CrCl less than 50 mL/min and were included in our review. Fondaparinux was stopped in all patients as none had proven HIT, and for this reason heparin was restarted. The duration of treatment with fondaparinux was 1.8 to 6.5 days, and it was administered SC ($n = 2$) or as a continuous IV infusion ($n = 3$) for the treatment of suspected HIT. All patients received 2.5 mg daily, except for one who received 1.25 mg daily due to previous postoperative bleeding complications. This patient was on high-volume continuous venovenous hemofiltration and was found to have an undetectable anti-Xa level, which may be due to a high extraction ratio of fondaparinux, in addition to the low dose received. A negative correlation was identified between CrCl and the mean anti-Xa level ($r = -.86$, $P = .028$). Number and severity of bleeding episodes with heparin before and after starting fondaparinux, respectively, were the following: 5 major and zero minor versus zero major and 2 minor bleeds, $P = .048$. Two major bleeding episodes were reported after stopping fondaparinux. No thromboembolic complications were reported. Two out of 7 patients had no recovery of their platelet count after stopping fondaparinux and died. One died due to septic shock with multiple organ failure. The other developed right hemothorax during heparin therapy after coronary artery bypass grafting and mitral valve annuloplasty. This study had a number of limitations. First, the sample size was small, and there was no control group. In addition, the fondaparinux treatment protocol was not submitted to the institution of medical ethics committee, and patients were only informed that their data were being collected for evaluation, without providing them with consent forms to sign. Although all patients were suspected to have HIT, none tested positive using the enzyme-linked immunosorbent assay. Furthermore, the majority of patients' platelet counts recovered even after restarting heparin, which may question the efficacy of fondaparinux as these patients were less likely to be in a HIT-associated procoagulative state.

In an RCT (OASIS-5) subgroup analysis,²⁰ 5141 patients with non-ST elevation acute coronary syndrome (non-STE ACS) and CrCl < 58 mL/min/1.73 m² were randomized to either enoxaparin 1 mg/kg twice daily (or once daily if CrCl < 30 mL/min/1.73 m²) or fondaparinux 2.5 mg once daily. There was no mention of how exactly the kidney function for these patients was subcategorized. The primary efficacy objective of the trial was to assess superiority of fondaparinux compared with enoxaparin to prevent death, myocardial infarction (MI), or refractory ischemia up to day 9. Whereas the primary safety outcome was to assess superiority of fondaparinux compared with enoxaparin in reducing major

bleeding at day 9. Aspirin was used in 96.8% ($n = 4974$) and clopidogrel or ticlopidine was used in 63% ($n = 3240$) of patients. Death, MI, and refractory ischemia were significantly lower in the fondaparinux group compared with the enoxaparin group at day 9 (10% vs 12.2%, hazard ratio = 0.81 [95% confidence interval (CI) = 0.69-0.96], $P = .01$). In relation to safety outcome, the fondaparinux group had significantly lower major bleeding events compared to enoxaparin at days 9 (2.8% vs 6.4%), 30 (4.2% vs 7.6%), and 180 (5.8% vs 8.7%), with hazard ratio (95% CI) of 0.42 (0.32-0.56), 0.54 (0.42-0.68), and 0.65 (0.52-0.80), respectively. In addition, the composite outcome (death, MI, refractory ischemia, and major bleeding) was significantly lower in fondaparinux group at days 9 (8.8% vs 12.5%), 30 (12.9% vs 17.6%), and 180 (21.3% vs 24.7%), and hazard ratio (95% CI) of 0.69 (0.58-0.82), 0.71 (0.62-0.82), and 0.83 (0.74-0.93), respectively. Interestingly, the net benefits of using fondaparinux in non-STE ACS compared with enoxaparin were most marked in patients with CrCl < 58 mL/min/1.73 m² ($n = 2561$ vs 2580, respectively). In this trial, the authors did not provide data regarding anti-Xa levels, and they used a fixed dose of fondaparinux regardless of whether patients developed a further decline in renal function or not. Finally, they excluded patients with serum creatinine > 3 mg/dL (CrCl ~ 20 mL/min/1.73 m² or less), which might have provided more data in such population.

PROFICE¹⁶ was a prospective cohort study that included 442 patients with CrCl between 20 and 50 mL/min (using Cockcroft-Gault formula) undergoing total hip or knee replacement or hip fracture surgery. Fondaparinux 1.5 mg SC daily was administered as thromboprophylaxis. The primary outcome was major bleeding until day 10 ± 2 , whereas the secondary outcomes were major bleeding up to day 30 ± 5 and nonmajor bleeding with clinical relevance, symptomatic VTE, and death until day 10 ± 2 and day 30 ± 5 . More than 85% of patients were above 75 years of age, 79.9% of patients were females, and 39.4% had poor physical status as defined by American Society of Anesthesiologists (ASA) score of 3 or more. In addition, 26.9% of patients had ≥ 1 additional risk factor for thromboembolism (history of cancer, DVT/PE, or stroke) and 77.6% had ≥ 1 additional risk factor for bleeding (history of cancer, diabetes, hypertension, gastric ulcer, or bleeding). The number of patients who had CrCl of 20 to 30, 30 to 40, and 40 to 50 mL/min were 64 (14.5%), 148 (33.5%), and 215 (48.6%), respectively, and fondaparinux was administered at a fixed dose to all patients regardless of renal function. Twenty patients (4.5%) developed major bleeding up until day 10, and a total of 23 (5.2%) had major bleeding at the end of study period; none was fatal or warranted treatment cessation. Three patients (0.7%) developed distal DVT during the study period. Using univariate analysis, CrCl was not associated with increased major bleeding at day 10 ± 2 . On the other hand, the combined factor male gender with ASA score > 3 on multivariate analysis was found statistically significant in terms of major bleeding (odds ratio

[OR] = 6.22; 95% CI = 2.27-17.1; $P = .002$). However, the percentage of male patients in comparison to females was small (about 20%). The study did not report anti-Xa levels, although patients were renally impaired and a fixed dose was used despite different renal functions between patients. In addition, there was no control group and the study was also funded by GlaxoSmithKline.

Cegarra-Sanmartin et al²¹ conducted a retrospective cohort study on 15 postoperative cardiac patients suspected to have HIT. Eleven patients were on continuous venovenous hemodiafiltration (CVVHDF), 1 patient was on hemodialysis (HD), 2 patients had CrCl of 45 mL/min, and 1 patient had CrCl >60 mL/min who was excluded from our review. The mean of age was 64 years, with a range of 30 to 77 years. Ten patients received initial treatment dose of 2.5 mg IV and one received 3 mg IV with target anti-Xa of 0.4 to 1.0 IU/mL. On the other hand, 2 patients received an initial prophylactic dose of 1.5 mg IV and 1 patient received 1.25 mg IV with a target anti-Xa of 0.2 to 0.4 IU/mL. After the initial dose, dose adjustment was made based on anti-Xa levels. If anti-Xa was lower or higher than the established range, the dose was doubled or halved, respectively. Two patients developed bleeding while on fondaparinux therapy, although anti-Xa levels were within target range. One of them was on HD who had acute pancreatitis and developed systemic inflammatory response state and respiratory failure. Consequently, thoracocentesis was performed 8 hours after stopping fondaparinux, which led to massive, fatal hemothorax. Such an event could be related to the slower rate of elimination of the medication using intermittent HD compared with CVVHDF. In this study, HIT was not confirmed, which might question the efficacy of fondaparinux. Additionally, the ultrafiltration and dialysate flow rates were not standardized, which might have affected the rate of medication clearance. Finally, the number of patients was small.

Discussion

In our review, a total of 3237 patients received fondaparinux, of which 470 experienced VTE, 169 had major bleeding, and 13 had minor bleeding events. The number of patients who developed major bleeding is half of those who developed thromboembolism; however, we cannot confirm this finding due to the differences in the population, doses, degree of kidney impairment, and indications of fondaparinux between both groups.

There are different dosing regimens for fondaparinux under normal renal function. For treating DVT, PE, and HIT, 5 mg, 7.5 mg, or 10 mg once daily is used if the patient's weight is <50 kg, 50 to 100 kg, or >100 kg, respectively.^{12,22} The 2.5 mg dose is used for the treatment of acute coronary syndrome²³ and as thromboprophylaxis postoperatively.¹² In this review, a total of 659 patients received fondaparinux 1.5 mg daily for the prevention of VTE, and 2576 patients received 2.5 mg daily as treatment dose. From the group who

were given 1.5 mg, 13 patients (2%) had thromboembolism and 25 (3.8%) had major bleeding events. In the 2.5 mg group, 452 patients (17.5%) developed thromboembolism and 144 (5.6%) had major bleeding events. In these studies, fondaparinux prophylactic dose was reduced by about 50% of the recommended normal dose. In contrast, OASIS-5²⁰ patients received normal fondaparinux dose of 2.5 mg for non-STE ACS. Cegarra-Sanmartin et al²¹ and Wester et al¹⁹ treated their patients with half the 5 mg dose used for treating HIT under normal kidney function. Such a dose is used for patients <50 kg, but the weight was not reported in both studies. Overall, VTE and major bleeding events were lower with the prophylactic adjusted dose (1.5 mg) compared with the treatment dose used in the OASIS-5 trial, but it is not clear whether 1.5 mg dose should be considered safer and more effective as prophylactic dose compared to the 2.5 mg treatment dose used for non-STE ACS in patients with renal impairment, and needs more controlled trials. In addition, there was variation in estimating CrCl among the studies. Two studies used the MDRD formula,^{18,20} 1 study used the urine creatinine method,¹⁹ and 2 studies used the Cockcroft-Gault equation.^{16,17} In one pharmacokinetic study, the MDRD formula was found to be more accurate than the Cockcroft-Gault in describing kidney function-fondaparinux clearance relationship.²⁴

Three^{17,19,21} out of 6 studies reported anti-Xa levels, which might guide anticoagulant therapy in patients with renal impairment since the dose under such condition is not well established. In these studies, 4 patients developed bleeding events although anti-Xa was on target, which might indicate bleeding due to anticoagulant accumulation that is not reflected by anti-Xa activity. Based on the manufacturer's recommendation, only fondaparinux should be used to calibrate anti-Xa assay in samples drawn from patients given fondaparinux. Heparin and low-molecular-weight heparins are considered to be inappropriate.¹² Nevertheless, only one study¹⁹ reported using anti-Xa assay calibrated for fondaparinux.

One of the limitations of our review was the limited number of studies that reported the use of fondaparinux in renal impairment. Additionally, OASIS-5 trial was the only study that had a control group (enoxaparin), while others included the fondaparinux group as the only arm. Certain studies lacked some data that limited further interpretation of their results, especially subcategorizing of CrCl and its impact on reported safety and efficacy of fondaparinux. Our review was not comprehensive as we did not include case reports and case series, as we thought the small sample size of each report will not contribute significantly to the larger studies already included. Furthermore, we only included MEDLINE and Cochrane databases in our review.

Summary

Current evidence regarding safe and effective use of fondaparinux in moderate-to-severe renal impairment is

still weak. We recommend using fondaparinux 1.5 mg SC once daily for the VTE prevention. In case of treatment, other anticoagulants that do not need renal adjustment, like heparin and argatroban, should be used.

Acknowledgment

The authors thank Dr Lama H. Nazer for reviewing the article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis.* 2012;60:850-886.
2. Centers for Disease Control and Prevention. 2014 National chronic kidney disease fact sheet. <http://www.cdc.gov/diabetes/pubs/factsheets/kidney.htm>. Accessed June 30, 2014.
3. Choi HS, Sung KC, Lee KB. The prevalence and risk factors of microalbuminuria in normoglycemic, normotensive adults. *Clin Nephrol.* 2006;65:256-261.
4. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. *J Am Soc Nephrol.* 2003;14(7 suppl 2):S131-S138.
5. Magnason RL, Indridason OS, Sigvaldason H, Sigfusson N, Palsson R. Prevalence and progression of CRF in Iceland: a population-based study. *Am J Kidney Dis.* 2002;40:955-963.
6. Garg AX, Mamdani M, Juurlink DN, van Walraven C; Network of Eastern Ontario Medical Laboratories (NEO-MeL). Identifying individuals with a reduced GFR using ambulatory laboratory database surveillance. *J Am Soc Nephrol.* 2005;16:1433-1439.
7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 suppl 1):S1-S266.
8. Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol.* 2008;19:135-140.
9. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation.* 2003;107:87-92.
10. Sood MM, Komenda P, Sood AR, Rigatto C, Bueti J. The intersection of risk and benefit: is warfarin anticoagulation suitable for atrial fibrillation in patients on hemodialysis? *Chest.* 2009;136:1128-1133.
11. Bauer KA. New pentasaccharides for prophylaxis of deep vein thrombosis: pharmacology. *Chest.* 2003;124(6 suppl):364S-370S.
12. GlaxoSmithKline. Arixtra (fondaparinux) prescribing information. Research Triangle Park, NC, GlaxoSmithKline; September 2013.
13. Turpie AG, Gallus AS, Hoek JA; Pentasaccharide Investigators. A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement. *N Engl J Med.* 2001;344:619-625.
14. Garcia DA, Baglin TP, Weitz JI, Samama MM; American College of Chest Physicians. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e24S-e43S.
15. European Medicines Agency. EMEA/H/C/000403-IAin/0064/G: Arixtra product information. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000403/WC500027746.pdf. Accessed October 31, 2014.
16. Mismetti P, Samama CM, Rosencher N, et al. Venous thromboembolism prevention with fondaparinux 1.5 mg in renally impaired patients undergoing major orthopaedic surgery. A real-world, prospective, multicentre, cohort study. *Thromb Haemost.* 2012;107:1151-1160.
17. Hester W, Fry C, Gonzalez D, Cohen-Wolkowicz M, Inman BA, Ortel TL. Thromboprophylaxis with fondaparinux in high-risk postoperative patients with renal insufficiency. *Thromb Res.* 2014;133:629-633.
18. 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.
19. Wester JP, Leyte A, Oudemans-van Straaten HM, et al. Low-dose fondaparinux in suspected heparin-induced thrombocytopenia in the critically ill. *Neth J Med.* 2007;65(3):101-108.
20. Fox KA, Bassand JP, Mehta SR, et al. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non ST-segment elevation acute coronary syndromes. *Ann Intern Med.* 2007;147:304-310.
21. Cegarra-Sanmartin V, Gonzalez-Rodriguez R, Paniagua-Iglesias P, et al. Fondaparinux as a safe alternative for managing heparin-induced thrombocytopenia in postoperative cardiac surgery patients. *J Cardiothorac Vasc Anesth.* 2014;28:1020-1024. doi:10.1053/j.jvca.2013.09.008.
22. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 suppl):e495S-e530S.
23. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2013;127:e663-e828.
24. Delavanne X, Zufferey P, Baylot D, et al. Population pharmacokinetics of fondaparinux administered at prophylactic doses after major orthopaedic surgery in everyday practice. *Thromb Haemost.* 2010;104:252-260.