

IN THE LITERATURE

Efficacy and Safety of Fondaparinux and Enoxaparin for Acute Coronary Syndromes in CKD

Commentary on 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 147:304-310, 2007.

Patients with chronic kidney disease (CKD) have high rates of traditional cardiac risk factors, such as advanced age, hypertension, diabetes mellitus, left ventricular hypertrophy, and dyslipidemia. They also have a high prevalence of nontraditional cardiac risk factors, such as anemia, proteinuria, electrolyte imbalances, hyperhomocysteinemia, and vascular dysfunction.¹ Not surprisingly, coronary heart disease is highly prevalent in this population, and it is the leading cause of death in dialysis patients, as well as those with earlier stages of CKD.² Dialysis patients are more than 10 to 30 times as likely to die of this complication compared with the general population.¹

Given the high prevalence of acute coronary syndrome (ACS) in patients with CKD, clinicians frequently are confronted with choosing an appropriate antithrombotic regimen that both maximizes clinical benefit and minimizes bleeding risk during percutaneous coronary intervention (PCI). Use of enoxaparin and unfractionated heparin in patients with decreased kidney function have both been associated with increased bleeding risk.³⁻⁵

Fondaparinux, a synthetic pentasaccharide anticoagulant, has selective antithrombin and anti-factor Xa activity. It has proven thromboprophylaxis benefits over enoxaparin in orthopedic surgery⁶ and has been found to be noninferior to unfractionated heparin in treating patients with pulmonary embolism⁷ and deep vein thrombosis.⁸ Although not currently approved by the US Food and Drug Administration (FDA) for treatment of patients with ACS and PCI, preliminary data suggest that fondaparinux has efficacy similar to enoxaparin⁹ and less frequent bleeding complications than unfractionated heparin¹⁰ in patients with normal kidney function. Fondaparinux is eliminated unchanged in urine, whereas enoxaparin undergoes both hepatic metabolism and urinary excretion. The difference in drug elimination may have important consequences in patients with CKD. Recently, 2 reports of the Fifth Organization to Assess Strategies in Acute

Ischemic Syndromes (OASIS-5) trial compared the efficacy and safety of these compounds in PCI for patients with ACS.

WHAT DID THIS IMPORTANT STUDY SHOW?

OASIS-5 was a multinational, randomized, double-blind, placebo-controlled, parallel-group study of fondaparinux versus enoxaparin in patients with unstable angina or non-ST-segment elevation myocardial infarction.¹¹ Briefly, OASIS-5 compared the safety and effectiveness of enoxaparin, 1 mg/kg, subcutaneously every 12 hours with fondaparinux, 2.5 mg, subcutaneously once daily in 20,078 patients within 24 hours after the onset of unstable angina or non-ST-segment elevation myocardial infarction. In patients with a creatinine clearance (C_{Cr}) less than 30 mL/min, the enoxaparin dose was decreased to 1 mg/kg once daily; there were no dose adjustments for fondaparinux. Fondaparinux and enoxaparin could be administered for up to 8 days or until patient discharge. The primary objectives of the study were to: (1) show the noninferiority of fondaparinux compared with enoxaparin in the primary efficacy end point (death, myocardial infarction, or refractory ischemia) at 9 days; and (2) determine whether the safety profile of fondaparinux was superior to that of enoxaparin with respect to major bleeding. Patients were fol-

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lowed up for a minimum of 90 days and a maximum of 180 days.

The main results were reported in the April 6, 2006, edition of the *New England Journal of Medicine*.¹¹ Fondaparinux and enoxaparin had similar composite cardiac event rates at 9, 30, and 180 days. However, fondaparinux had significantly lower bleeding rates at 9 days (2.2% versus 4.1%, respectively; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.44 to 0.61; $P < 0.001$), 30 days (3.1% versus 5.0%, respectively; HR, 0.62; 95% CI, 0.54 to 0.72; $P < 0.001$), and 180 days (4.3% versus 5.8%, respectively; HR, 0.72; 95% CI, 0.64 to 0.82; $P < 0.001$). The investigators concluded that fondaparinux had efficacy similar to enoxaparin in decreasing the risk of cardiac ischemia at 9 days and had a significantly lower risk of bleeding.

In the September 4, 2007, edition of the *Annals of Internal Medicine*,¹² this same investigative team published a subgroup analysis of these data to assess whether the increased bleeding risk noted with enoxaparin in OASIS-5 was related to the level of kidney function in study participants. Therefore, the efficacy and safety data from 19,979 OASIS-5 participants were stratified into quartiles based on estimated glomerular filtration rate ([eGFR]: < 58 (N = 5,141); 58 to 71 (N = 4,845); 71 to 86 (N = 5012); and ≥ 86 mL/min/1.73 m² (N = 4,996), respectively).

Regarding efficacy, fondaparinux had a significant benefit in decreasing the composite outcome of death, myocardial infarction, and refractory ischemia at day 30 only in patients with eGFR less than 58 mL/min/1.73 m². All other eGFR groups had similar end point rates compared with enoxaparin. However, regarding safety, fondaparinux use was associated with significantly lower bleeding events compared with enoxaparin (Table 1). At day 9, fondaparinux use was associated with less major bleeding across all eGFR quartiles. This continued through days 30 and 180 for all eGFR quartiles with the exception of eGFR of 71 to 85 mL/min/1.73 m². The most notable bleeding differences were found in those with an eGFR less than 58 mL/min/1.73 m² (Table 1). At day 9, the HR for major bleeding events in the fondaparinux group was less than half that of the enoxaparin group (HR, 0.42; 95%

CI, 0.32 to 0.56; $P < 0.001$) and continued to be significantly lower throughout the duration of the study (HR, 0.65; 95% CI, 0.52 to 0.80; $P < 0.001$ at 180 days).

HOW DOES THIS STUDY COMPARE WITH PRIOR STUDIES?

This is the first analysis specifically aimed at documenting the safety and efficacy of fondaparinux in patients with varying levels of kidney function; however, there have been analyses of enoxaparin in this population. A recent meta-analysis assessed the risk of bleeding and antifactor Xa levels in patients with stage 4 or non-dialysis-dependent stage 5 CKD treated with enoxaparin and other low-molecular-weight heparin preparations.³ In total, 18 clinical trials were analyzed; 8 focused solely on the use of therapeutic doses of enoxaparin (1 mg/kg every 12 hours or 1.5 mg/kg every 24 hours) in patients with a C_{Cr} of 30 mL/min or less,^{4,13-19} whereas 4 studies focused on adjusted-dose enoxaparin administration in patients with a C_{Cr} of 30 mL/min or less.²⁰⁻²³

Results of this meta-analysis showed 2 clinically significant findings: (1) a clear inverse relationship exists between C_{Cr} and peak antifactor Xa levels; and (2) the presence of a C_{Cr} of 30 mL/min or less was independently associated with increased risk of major bleeding events in patients receiving therapeutic-dose enoxaparin. For example, the odds ratio of severe bleeding in patients with a C_{Cr} of 30 mL/min or less receiving therapeutic enoxaparin dosing was nearly 4 times greater than that of patients with a greater C_{Cr} (odds ratio, 3.88; 95% CI, 1.78 to 8.45; $P = 0.03$). In the 4 studies that administered decreased doses of enoxaparin, there was no increase in adverse bleeding (odds ratio, 0.58; 95% CI, 0.09 to 3.78; $P = 0.5$). However, because the number of patients with a C_{Cr} less than 30 mL/min in these studies was small, these results should be interpreted with caution.

WHAT SHOULD CLINICIANS AND RESEARCHERS DO?

The OASIS-5 subgroup analysis provides encouraging clinical results. It suggests that fondaparinux has similar clinical efficacy and less major bleeding compared with enoxaparin,

Table 1. Efficacy and Safety Outcomes of Fondaparinux and Enoxaparin in the Subgroup Analysis of OASIS-5.

Outcome	No. of Randomly Assigned Patients	Overall	Enoxaparin Group	Fondaparinux Group	Hazard Ratio (95% CI)	P
Death, myocardial infarction, or refractory ischemia						
9 d						
GFR < 58 mL/min/1.73 m ²	5,141	363 (7.1)	191 (7.4)	172 (6.7)	0.90 (0.73-1.11)	0.32
GFR 58-<71 mL/min/1.73 m ²	4,845	297 (6.1)	140 (5.8)	157 (6.4)	1.10 (0.88-1.38)	0.41
GFR 71-<86 mL/min/1.73 m ²	5,012	235 (4.7)	116 (4.6)	119 (4.8)	1.03 (0.80-1.33)	0.81
GFR ≥ 86 mL/min/1.73 m ²	4,996	252 (5.0)	123 (4.9)	129 (5.2)	1.05 (0.82-1.34)	0.70
Interaction	—	—	—	—	—	0.38
30 d						
GFR < 58 mL/min/1.73 m ²	5,141	573 (11.1)	315 (12.2)	258 (10.0)	0.81 (0.69-0.96)	0.01
GFR 58-<71 mL/min/1.73 m ²	4,845	409 (8.4)	193 (8.1)	216 (8.8)	1.10 (0.90-1.33)	0.34
GFR 71-< 86 mL/min/1.73 m ²	5,012	317 (6.3)	163 (6.5)	154 (6.2)	0.95 (0.76-1.18)	0.65
GFR ≥ 86 mL/min/1.73 m ²	4,996	361 (7.2)	189 (7.6)	172 (6.9)	0.91 (0.74-1.12)	0.37
Interaction	—	—	—	—	—	0.45
180 d						
GFR < 58 mL/min/1.73 m ²	5,141	946 (18.7)	495 (19.6)	451 (17.9)	0.90 (0.79-1.03)	0.12
GFR 58-<71 mL/min/1.73 m ²	4,845	603 (12.6)	297 (12.6)	306 (12.7)	1.01 (0.86-1.19)	0.87
GFR 71-< 86 mL/min/1.73 m ²	5,012	467 (9.4)	245 (9.9)	222 (9.0)	0.91 (0.76-1.09)	0.30
GFR ≥ 86 mL/min/1.73 m ²	4,996	503 (10.2)	265 (10.7)	238 (9.6)	0.90 (0.75-1.07)	0.22
Interaction	—	—	—	—	—	0.85
Major bleeding events						
9 d						
GFR < 58 mL/min/1.73 m ²	5,141	233 (4.6)	163 (6.4)	70 (2.8)	0.42 (0.32-0.56)	<0.001
GFR 58-< 71 mL/min/1.73 m ²	4,845	170 (3.5)	110 (4.6)	60 (2.5)	0.53 (0.39-0.72)	<0.001
GFR 71-< 86 mL/min/1.73 m ²	5,012	123 (2.5)	74 (3.0)	49 (2.0)	0.66 (0.46-0.95)	0.026
GFR ≥ 86 mL/min/1.73 m ²	4,996	103 (2.1)	64 (2.6)	39 (1.6)	0.61 (0.41-0.90)	0.014
Interaction	—	—	—	—	—	0.056
30 d						
GFR < 58 mL/min/1.73 m ²	5,141	299 (5.9)	193 (7.6)	106 (4.2)	0.54 (0.42-0.68)	<0.001
GFR 58-< 71 mL/min/1.73 m ²	4,845	209 (4.4)	127 (5.4)	82 (3.4)	0.62 (0.47-0.82)	<0.001
GFR 71-< 86 mL/min/1.73 m ²	5,012	154 (3.1)	88 (3.5)	66 (2.7)	0.75 (0.55-1.03)	0.078
GFR ≥ 86 mL/min/1.73 m ²	4,996	145 (2.9)	85 (3.4)	60 (2.4)	0.70 (0.50-0.98)	0.036
Interaction	—	—	—	—	—	0.093
180 d						
GFR < 58 mL/min/1.73 m ²	5,141	359 (7.3)	216 (8.7)	143 (5.8)	0.65 (0.52-0.80)	<0.001
GFR 58-< 71 mL/min/1.73 m ²	4,845	260 (5.5)	147 (6.3)	113 (4.8)	0.74 (0.58-0.95)	0.018
GFR 71-< 86 mL/min/1.73 m ²	5,012	191 (3.9)	102 (4.1)	89 (3.6)	0.87 (0.66-1.16)	0.350
GFR ≥ 86 mL/min/1.73 m ²	4,996	177 (3.6)	103 (4.2)	74 (3.0)	0.71 (0.53-0.96)	0.026
Interaction	—	—	—	—	—	0.301

Note: Values expressed as number (percent) unless noted otherwise.

Abbreviations: OASIS-5, Fifth Organization to Assess Strategies in Acute Ischemic Syndromes; CI, confidence interval; GFR, glomerular filtration rate.

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especially in patients with decreased kidney function. With respect to bleeding, this finding is surprising given that both drugs undergo extensive renal clearance and have prolonged plasma half-lives in patients with CKD. There are at least 2 potential explanations for this. First, unlike fondaparinux, which is excreted unchanged in urine, enoxaparin undergoes some hepatic metabolism into active and inactive heparin fragments that also are renally cleared. This prolongs its half-life in patients with CKD and may explain the increased bleeding. Second, the fondaparinux dose administered in the OASIS-5 trial (2.5 mg) is the lowest available dose and is less than the typical 5- to 10-mg doses generally administered for patients with deep vein thrombosis and pulmonary embolism. Therefore, one could argue that the patients in the OASIS-5 study received at least a 50% dose reduction compared with standard fondaparinux therapy. This may serendipitously be the most appropriate dose in patients with CKD.

These efficacy and safety data, although compelling, have some noteworthy limitations that preclude fondaparinux from becoming standard-of-care treatment for patients with ACS and PCI with CKD. First, the vast majority of subjects (approximately 75%) had eGFRs typically not considered clinically relevant when dosing drugs (ie, eGFR > 60 mL/min/1.73 m²). The lowest eGFR quartile classification was less than 58 mL/min/1.73 m², and it was not clear how many of these patients truly had severe kidney disease (ie, eGFR < 30 mL/min/1.73 m²) versus moderate kidney disease (ie, eGFR, 30 to 59 mL/min/1.73 m²). It is possible that very few of these subjects had severe kidney disease; accordingly, it is unknown at this time how the efficacy and safety of fondaparinux would be influenced in patients with eGFR less than 30 mL/min/1.73 m². This analysis would have benefited if the investigators described the baseline level of kidney function in the subject demographics and then classified them according to accepted CKD stages.

Second, subgroup analyses can be prone to produce misleading results, particularly when subgroups in the analysis are not defined a priori. The OASIS-5 study was neither designed nor powered a priori to determine the efficacy and safety of fondaparinux and enoxaparin in patients with varying levels of kidney function.

Thus, these results should be considered exploratory and not confirmatory.

Third, at this time, fondaparinux is only FDA approved for the prophylaxis and treatment of patients with deep vein thrombosis and pulmonary embolism and is not approved for those with ACS. Because the practice of interventional cardiology has become highly evidence based and clinical practice guideline dominated, it is doubtful that cardiologists will routinely use non-FDA-approved drugs in highly complex procedures in high-risk patients, such as those with CKD.

Despite these limitations, this analysis touches on a key point that should be emphasized. Principally, to decrease the risk of bleeding, the therapeutic dose of enoxaparin should be decreased in patients with severe CKD. The FDA-approved package insert for enoxaparin suggests a dose decrease to 1 mg/kg subcutaneously once daily in patients with a C_{Cr} of 30 mL/min or less,²⁴ whereas others suggested alternative dose adjustments.²⁰⁻²³ The most appropriate dose decrease was not fully evaluated in the literature; therefore, at this time, it is prudent to follow the FDA-approved dosing guidelines and consider monitoring peak antifactor Xa levels to guide further dosing.

In conclusion, fondaparinux may be a safer alternative to enoxaparin in patients with decreased kidney function. These subgroup data provide a strong rationale for the development of additional large-scale analyses that assess the safety and efficacy of fondaparinux in patients with moderate to severe kidney disease.

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REFERENCES

1. Sarnak MJ, Levey AS, Schoolwerth AC, et al: AHA scientific statement: Kidney disease as a risk factor for development of cardiovascular disease. A statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 108:2154-2169, 2003

2. US Renal Data Systems: Morbidity and mortality, in USRDS 2006 Annual Data Report. *Am J Kidney Dis* 49: S130-S146, 2007 (suppl 1)
3. Lim W, Dentali F, Eikelboom JW, et al: Meta-analysis: Low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med* 144:673-684, 2006
4. Spinler SA, Inverso SM, Cohen M, et al: Safety and efficacy of unfractionated heparin versus enoxaparin in patients who are obese and patients with severe renal impairment: Analysis from the ESSENCE and TIMI 11B studies. *Am Heart J* 146:33-41, 2003
5. SYNERGY Trial Investigators: Enoxaparin vs. unfractionated heparin in high-risk patients with non-ST segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 292:45-54, 2004
6. Turpie AGG, Bauer KA, Eriksson BI, Lassen MR: Fondaparinux vs enoxaparin for the prevention of venous thromboembolism in major orthopaedic surgery: A meta-analysis of 4 randomized double-blind studies. *Arch Intern Med* 162:1833-1840, 2002
7. The Matisse Investigators: Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism [erratum in *N Engl J Med* 350:423, 2004]. *N Engl J Med* 349:1695-1705, 2003
8. Buller HR, Davidson BL, Decousus H, et al: Fondaparinux or enoxaparin for the initial treatment of symptomatic deep venous thrombosis: A randomized trial. *Ann Intern Med* 140:867-873, 2004
9. Simoons ML, Bobbink IWG, Boland J, et al: A dose-finding study of fondaparinux in patients with non-ST-segment elevation acute coronary syndromes: The Pentasaccharide in Unstable Angina (PENTUA) Study. *J Am Coll Cardiol* 43:2183-2219, 2004
10. Mehta SR, Steg PG, Granger CB, et al: Randomized, blinded trial comparing fondaparinux with unfractionated heparin in patients undergoing contemporary percutaneous coronary intervention: Arixtra Study in Percutaneous Coronary Intervention: A Randomized Evaluation (ASPIRE) Pilot Trial. *Circulation* 111:1390-1397, 2005
11. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators: Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med* 354:1464-1476, 2006
12. 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* 147:304-310, 2007
13. Chow SL, Zammit K, West K, Dannenhoffer M, Lopez-Candales A: Correlation of antifactor Xa concentrations with renal function in patients on enoxaparin. *J Clin Pharmacol* 43:586-590, 2003
14. Khazan M, Scheuering S, Adamson R, Mathis AS: Prescribing patterns and outcomes of enoxaparin for anticoagulation of atrial fibrillation. *Pharmacotherapy* 23:651-658, 2003
15. Macie C, Forbes L, Foster GA, Douketis JD: Dosing practices and risk factors for bleeding in patients receiving enoxaparin for the treatment of an acute coronary syndrome. *Chest* 125:1616-1624, 2004
16. Peng YG, Eikelboom JW, Tenni P, McQuillan A, Thom J: Renal function, peak anti-Xa levels and enoxaparin dosing. *J Pharm Pract Res* 34:14-17, 2004
17. Thorevska N, Amoateng-Adjepong Y, Sabahi R, et al: Anticoagulation in hospitalized patients with renal insufficiency: A comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest* 125:856-863, 2004
18. Bazinet A, Almanric K, Brunet C, et al: Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res* 116:41-50, 2005
19. Becker RC, Spencer FA, Gibson M, et al: Influence of patient characteristics and renal function on factor Xa inhibition pharmacokinetics and pharmacodynamics after enoxaparin administration in non-ST-segment elevation acute coronary syndromes. *Am Heart J* 143:753-759, 2002
20. Kruse MW, Lee JJ: Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J* 148:582-589, 2004
21. Green B, Greenwood M, Saltissi D, et al: Dosing strategy for enoxaparin in patients with renal impairment presenting with acute coronary syndromes. *Br J Clin Pharmacol* 59:281-290, 2005
22. Collet JP, Montalescot F, Fine E: Enoxaparin in unstable angina patients who would have been excluded from randomized clinical trials. *J Am Coll Cardiol* 41:8-14, 2003
23. Collet JP, Montalescot G, Choussat R, Lison L, Ankri A: Enoxaparin in unstable angina patients with renal failure. *Int J Cardiol* 80:81-82, 2001 (letter)
24. Sanofi-Aventis Pharmaceuticals: Lovenox (enoxaparin sodium) package insert. Sanofi-Aventis Pharmaceuticals, Bridgewater, NJ, 2006