

# Enoxaparin Outcomes in Patients With Moderate Renal Impairment

Douglas D. DeCarolis, PharmD; Joey G. Thorson, PharmD; Megan A. Clairmont, PharmD; Amy M. Leuthner, PharmD; Thomas S. Rector, PharmD, PhD; Gerhard J. Johnson, MD

**Background:** Enoxaparin sodium has predictable pharmacokinetics that allow for simplified dosing without laboratory monitoring. Reliance on renal function for excretion may lead to accumulation of enoxaparin in patients with moderate renal impairment. However, there is no dose adjustment recommended for these patients. We conducted a review to compare bleeding events in patients with moderate renal impairment compared with those with normal renal function.

**Methods:** Patients received enoxaparin sodium, 1 mg/kg, every 12 hours or 1.5 mg/kg once daily between June 1 and November 30, 2009. Moderate renal impairment was defined as creatinine clearance (CrCl) of 30 to 50 mL/min. Normal renal function was defined as CrCl greater than 80 mL/min. The primary outcome was major bleeding, defined as any bleeding resulting in death, hospital admission, lengthened hospital stay, or an emergency department visit. The secondary outcome was thromboembolism.

**Results:** A total of 164 patients met the inclusion criteria: 105 with normal renal function and 59 with moderate renal impairment. The primary outcome occurred in 6 of 105 patients (5.7%) with normal renal function vs 13 of 59 patients (22.0%) with moderate renal impairment, representing an unadjusted odds ratio of 4.7 (95% CI, 1.7-13.0;  $P = .002$ ). The odds ratio using multivariable logistic regression adjusting for differences in risk was 3.9 (95% CI, 0.97-15.6;  $P = .055$ ). There was no recurrent thromboembolism in either group.

**Conclusions:** Our results suggest an increased risk of major bleeding in patients with moderate renal impairment who receive enoxaparin. Because enoxaparin is frequently used and outcomes can be life saving or life threatening, we encourage further study of the appropriate dose in patients with moderate renal impairment.

*Arch Intern Med.* 2012;172(22):1713-1718.

Published online November 5, 2012.

doi:10.1001/2013.jamainternmed.369

**E**NOXAPARIN SODIUM, A LOW-molecular-weight heparin, has a predictable pharmacokinetic profile and dose-response curve, allowing simplified dosing without the need for vigilant monitoring through laboratory tests.<sup>1</sup> A disadvantage of enoxaparin is reliance on kidney function for excretion and potential accumulation of its anticoagulant effect in patients with declining renal function. The Food and Drug Administration–approved dosing recommends decreasing the daily dose by one-half in patients

a linear relationship between enoxaparin clearance measured by antifactor Xa activity and renal function measured by CrCl. Despite this linear relationship, there is no recommendation for dose adjustment for patients with moderate renal impairment (CrCl 30-50 mL/min). The package insert<sup>2</sup> recommends that these patients be observed carefully for signs and symptoms of bleeding but otherwise provides no guidance regarding dose adjustment or laboratory monitoring. In support of these concerns are reports<sup>9-14</sup> of increased bleeding in patients with moderate renal impairment who receive the recommended enoxaparin dose.

**Author Affiliations:** Pharmacy Service (Drs DeCarolis, Thorson, Clairmont, and Leuthner), Center for Chronic Disease Outcomes Research (Dr Rector), and Hematology/Oncology Section (Dr Johnson), Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota.

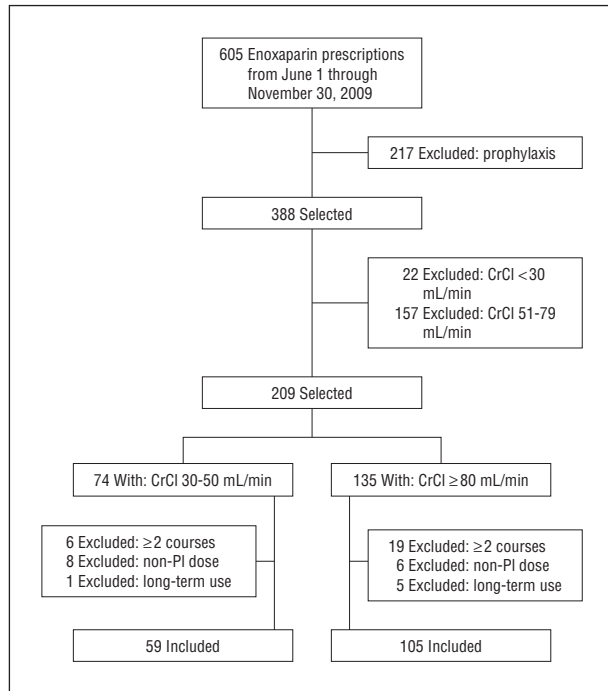


CME available online at [www.jamaarchivescme.com](http://www.jamaarchivescme.com) and questions on page 1702

with severe renal impairment, defined as creatinine clearance (CrCl) of less than 30 mL/min (to convert to milliliters per second, multiply by 0.0167).<sup>2</sup> The manufacturer's package insert<sup>2</sup> and pharmacokinetic studies<sup>3-8</sup> have consistently described

*See Invited Commentary at end of article*

Enoxaparin's risk-benefit profile balances treatment of thrombosis with risk of bleeding, both of which can be of major significance. Enoxaparin use in patients with moderate renal impairment re-



**Figure.** Inclusion and exclusion criteria of patients. CrCl indicates creatinine clearance; PI, package insert. To convert CrCl to milliliters per second, multiply by 0.0167.

sults in a higher concentration of the anticoagulant; however, the recommended dose remains the same as with normal renal function. Ensuring an accurate dose may have significant influence on relevant outcomes. Therefore, appropriate dose modification would appear necessary to maintain a proper balance of efficacy and safety in patients with reduced renal function. The large-scale clinical studies instrumental in the approval of current dosing enrolled healthier patient populations than those seen in everyday clinical practice and often excluded patients with renal dysfunction. Smaller studies<sup>7,15-17</sup> have made dose modifications to target an antifactor Xa activity therapeutic range, despite a lack of strong evidence correlating antifactor Xa activity target range to outcomes.<sup>18,19</sup> Thus, we conducted a review of medical records to compare the outcomes of bleeding and recurrent thrombotic events in patients with normal renal function vs those with moderate renal impairment who were receiving the manufacturer's recommended therapeutic dose of enoxaparin.

## METHODS

This study was performed at the Minneapolis Veterans Affairs Health Care System (MVAHCS), a tertiary care teaching facility that provides inpatient and primary and subspecialty ambulatory care. An electronic medical record documents dispensing of outpatient medications, administration of inpatient medications, laboratory test results, and clinical progress notes. The electronic medical record provides access to data from other VA medical facilities, allowing follow-up of clinical status when primary care is transferred. Because the VA serves as the primary care provider of most patients, admissions to other hospitals or emergency department visits are documented in the electronic medical record when this information is made available or telephone contact is made. The MVAHCS uses an enox-

aparin protocol that requires baseline laboratory data and body weight to be documented before treatment. These data permit clinical pharmacists to calculate the dose on the basis of current product labeling and evidence-based guidelines.<sup>1,2</sup> Deviation from this dose requires approval via the hematology consult service.

Patients who received enoxaparin between June 1 and November 30, 2009, during a hospital inpatient stay or as an outpatient prescription were identified via dispensing records. Patients were excluded if they received enoxaparin for venous thromboembolism prophylaxis, dosing differed from that in the manufacturer's package insert, or long-term enoxaparin therapy was prescribed. Long-term therapy was defined as a regimen in which enoxaparin is the anticoagulant to be used for the full duration of treatment. Thus, our study concentrated on the use of enoxaparin for initiation of parenteral anticoagulation as well as for bridge therapy, both with planned transition to oral anticoagulation therapy (warfarin sodium). Initiation of anticoagulation was defined as treatment for a new thrombotic indication with eventual transitioning to oral anticoagulation. Bridge therapy was defined as transitioning from a therapeutic level of oral anticoagulation followed by interruption and replacement with therapeutic doses of enoxaparin, with a planned transition back to oral anticoagulation. For patients who received more than 1 course of enoxaparin during this period, only the first course was included in the analysis.

The main objective of our study was to compare major bleeding outcomes in patients with normal renal function vs those with moderate renal impairment receiving the product-labeled enoxaparin dose. Normal renal function was defined as CrCl greater than 80 mL/min, and moderate renal impairment was defined as CrCl OF 30 to 50 mL/min.<sup>2</sup> Our final study population consisted of patients who received enoxaparin sodium at a therapeutic dosage of 1 mg/kg of body weight every 12 hours or 1.5 mg/kg every 24 hours and estimated CrCl as specified. Creatinine clearance was calculated using the Cockcroft-Gault formula with lean body weight.<sup>20,21</sup> The actual body weight was used to calculate the enoxaparin dose.

The following data were extracted from the electronic medical record: enoxaparin indication, dose, and duration of therapy; age; sex; race; weight; levels of serum creatinine, alanine aminotransferase, aspartate aminotransferase, and hemoglobin; platelet count; baseline international normalized ratio; and highest international normalized ratio during enoxaparin therapy. Baseline risk factors for bleeding were collected, including history of uncontrolled hypertension, cancer, cerebrovascular accidents, bleeding, falls, or recent trauma or surgery and the World Health Organization performance score.<sup>22,23</sup> Concurrent medications 7 days before or during enoxaparin therapy, including antiplatelet agents, nonsteroidal anti-inflammatory drugs, fish oil, vitamin E, and warfarin, were recorded as risk factors.<sup>22</sup>

An extensive medical record review was conducted to assess outcome data that included the 14 days following completion of enoxaparin therapy. The primary outcome of the study was major bleeding, defined as any bleeding resulting in hospital admission or death, lengthened hospital stay, or an emergency department visit. The secondary outcome was any evidence of new, progressing, or recurring thromboembolism during the same period. The protocol was approved by the MVAHCS institutional review board.

Characteristics of the patients categorized according to CrCl were described using means (SDs) or proportions (percentiles). An odds ratio for a bleeding episode was estimated with 95% CIs, using logistic regression to adjust for differences at baseline other than renal function that might have represented a substantial difference in the risk of bleeding. Commercial software (Stata, version 10.1; StataCorp) was used for all analyses.

**Table 1. Baseline Characteristics of Patients Grouped by CrCl**

Characteristic	No. (%)	
	CrCl ≥80 mL/min (n = 105)	CrCl 30-50 mL/min (n = 59)
Age, mean (SD), y	61 (9.9)	76 (9.8)
Men	101 (96)	58 (98)
ABW, mean (SD), kg	94.8 (21.4)	91.9 (21.6)
SCr, mean (SD), mg/dL	0.82 (0.16)	1.46 (0.41)
CrCl, mean (SD), mL/min	104.1 (26.0)	42.8 (6.0)
New diagnosis vs bridge therapy		
New anticoagulation therapy	40 (38.1)	22 (37.3)
Bridge therapy <sup>a</sup>	65 (61.9)	37 (62.7)
Bleeding risk factors		
SBP ≥200 mm Hg	1 (1.0)	3 (5.1)
Active cancer	19 (18.1)	8 (13.6)
History of CVA	11 (10.5)	9 (15.3)
Diabetes mellitus	33 (31.4)	21 (35.6)
History of major bleeding	11 (10.5)	7 (11.9)
Recent surgery or trauma	26 (24.8)	11 (18.6)
AST or ALT ≥3 × ULN	9 (8.6)	0
Platelet count <100 × 10 <sup>3</sup> /μL	3 (2.9)	4 (6.8)
Hemoglobin level <10 mg/dL	14 (13.3)	7 (11.9)
Baseline INR, mean (SD)	1.66 (0.82)	1.73 (0.89)
Baseline INR ≥2.0	31 (29.5)	16 (27.1)
Length of therapy, mean (SD), d	12.8 (11.9)	11.9 (11.2)
Highest INR during enoxaparin sodium therapy, mean (SD)	2.84 (1.23)	2.52 (1.28)
Enoxaparin sodium dosage		
1 mg/kg every 12 h	103 (98.1)	59 (100)
1.5 mg/kg every 24 h	2 (1.9)	0
Concomitant medications <sup>b</sup>		
Aspirin	54 (51.4)	36 (61.0)
Clopidogrel bisulfate	11 (10.5)	4 (6.8)
Aspirin and clopidogrel	9 (8.6)	2 (3.4)
Warfarin sodium	92 (87.6)	55 (93.2)
Aspirin, clopidogrel, and warfarin	4 (3.8)	1 (1.7)
NSAID	17 (16.2)	2 (3.4)
Fish oil, ≥2 g/d	13 (12.4)	7 (11.9)

Abbreviations: ABW, actual body weight; ALT, alanine transaminase; AST, aspartate transaminase; CrCl, creatinine clearance (calculated using the Cockcroft-Gault equation); CVA, cerebrovascular accident; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; SBP, systolic blood pressure; SCr, serum creatinine; ULN, upper limit of normal.

SI conversion factors: To convert SCr to micromoles per liter, multiply by 88.4; CrCl to milliliters per second, multiply by 0.0167; platelet count to × 10<sup>9</sup>/L, multiply by 1; and hemoglobin to grams per liter, multiply by 10.

<sup>a</sup>Bridge therapy was defined as transitioning from a therapeutic level of oral anticoagulation followed by interruption of oral anticoagulation and replacement with therapeutic doses of enoxaparin, with a planned transition back to oral anticoagulation.

<sup>b</sup>No patients received more than 400 IU of vitamin E 7 days before or during enoxaparin therapy.

## RESULTS

A total of 605 enoxaparin courses were identified during the 6-month study period. Inclusion and exclusion data are illustrated in the **Figure**. The final sample consisted of 164 patients: 105 with normal renal function and 59 with moderate renal impairment.

Baseline characteristics are summarized in **Table 1**. In addition to the selected differences in renal function,

**Table 2. Indications for Enoxaparin Sodium Therapy**

Indication	New Anticoagulation Therapy Started (n = 62)	Bridge Therapy (n = 102)
	Venous thromboembolism	45
Atrial fibrillation	7	32
Mechanical heart valve	0	30
Acute coronary syndrome	6	0
Arterial thrombosis, PAD	4	3

Abbreviation: PAD, peripheral artery disease.

**Table 3. Major Bleeding per Indication for Bridge Therapy<sup>a</sup>**

Indication	No./No. (%)		
	Major Bleeding	CrCl ≥80 mL/min	CrCl 30-50 mL/min
Invasive procedure for diagnosis or treatment <sup>b</sup>	5/31 (16.1)	1/15 (6.7)	4/16 (25.0)
Surgical procedure	3/28 (10.7)	1/20 (5.0)	2/8 (25.0)
Anticoagulation during unplanned, subtherapeutic oral anticoagulation therapy	1/26 (3.8)	1/19 (5.3)	0/7 (0)
Cardiac ablation procedure	5/17 (29.4)	2/11 (18.2)	3/6 (50.0)

Abbreviation: CrCl, creatinine clearance.

SI conversion factor: To convert CrCl to milliliters per second, multiply by 0.0167.

<sup>a</sup>Major bleeding was defined as any bleeding resulting in hospital admission or death, lengthened hospital stay, or an emergency department visit directly attributed to the bleeding.

<sup>b</sup>Angiography, automatic insertable cardioverter-defibrillator placement, endoscopic retrograde cholangiopancreatography, esophagogastroduodenoscopy, colonoscopy, and biopsy.

the group with moderate renal impairment was older and had a greater percentage with platelet counts less than 100 × 10<sup>3</sup>/μL (1:1 conversion to × 10<sup>9</sup>/L). The normal renal function group had a greater percentage with elevated liver enzyme levels. The mean baseline international normalized ratio was similar between the groups, as were baseline risk factors and use of bridge therapy. The mean duration of enoxaparin treatment was slightly longer in the normal renal function group (12.8 days vs 11.9 days). A greater percentage of patients with normal renal function were taking a nonsteroidal anti-inflammatory drug.

The primary outcome of major bleeding occurred in 6 of 105 patients (5.7%) with normal renal function vs 13 of 59 patients (22.0%) with moderate renal impairment. There were no deaths. The unadjusted odds ratio for major bleeding was 4.7 (95% CI, 1.7-13.0; *P* = .002). With adjustment for differences in risk factors using multivariable logistic regression, the odds ratio was 3.9 (95% CI, 0.97-15.6; *P* = .055). There was no recurrent thromboembolism.

Indications for enoxaparin anticoagulation therapy are presented in **Table 2**. More bleeding occurred in pa-

tients undergoing bridge therapy vs new anticoagulation (13.7% vs 8.1%). This trend was similar in both renal function groups. Reasons for bridging therapy and bleeding outcomes are reported in **Table 3**. A high frequency of major bleeding (5 of 17 patients [29.4%]) was noted in patients undergoing cardiac ablation procedures receiving bridge therapy with standard doses of enoxaparin. When these procedures were excluded, the overall incidence of major bleeding remained substantial (18.9%) in the group with moderate renal impairment.

## COMMENT

This study evaluated the safety of enoxaparin administered in recommended doses to patients with moderate renal impairment. The results reveal a disturbing rate of major bleeding in 1 of 4.5 patients with moderate renal impairment, constituting an odds ratio of 4.7, compared with patients with normal renal function. Bleeding severe enough to require hospital admission occurred in 1 of 7.5 patients in the group with moderate renal impairment. This rate of major bleeding is substantially higher than that in the large trials<sup>24-31</sup> of enoxaparin. Of note, these large trials included homogeneous patient groups (ie, 1 indication), multiple exclusions, and short durations of enoxaparin therapy. In contrast, our study was longer and is more representative of everyday, real-world practice of using enoxaparin for mixed indications and longer duration, with concomitant antiplatelet or anticoagulant agents, varied renal function, and bridging therapy.

Our results are consistent with those of other studies that showed increased bleeding in patients with moderate renal impairment. A pharmacokinetic-pharmacodynamic analysis of the Thrombolysis in Myocardial Infarction (TIMI) 11A trial<sup>9</sup> revealed the risk of hemorrhage to be strongly associated with moderate renal impairment. Enoxaparin clearance was reduced by 21% in this subgroup and the risk of a major hemorrhagic event was increased 1.4 to 2.8 times. Thorevska et al<sup>10</sup> reported an 11% incidence of major bleeding with use of manufacturer-recommended doses in patients with moderate renal impairment. Barras et al<sup>12</sup> demonstrated that 23% of patients with moderate renal impairment receiving the manufacturer-recommended therapeutic dose of enoxaparin experienced major bleeding, a result strikingly similar to ours. The Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS-5) trial<sup>32</sup> documented increased bleeding events as renal function progressively declined below an estimated glomerular filtration rate of 58 mL/min/1.73 m<sup>2</sup> and revealed renal function to be an important independent determinant of major bleeding. Each 10-mL/min decrement of CrCl was associated with increased bleeding risk when enoxaparin was used with thrombolytics for the treatment of ST-segment elevation myocardial infarction.<sup>14</sup> In a multivariate regression model, CrCl remained an independent risk factor for intracranial and major bleeding, leading these authors to suggest an empirical dose adjustment to maintain the best risk-benefit ratio.<sup>14</sup>

The mechanism responsible for increased bleeding in patients with reduced renal function appears to be increased anticoagulant effect secondary to drug accumula-

tion. Studies<sup>5-7,9,15,17,33</sup> evaluating enoxaparin pharmacokinetics via antifactor Xa activity have consistently shown increased drug half-life and accumulation of antifactor Xa activity in patients with moderate renal impairment. The consensus of these studies is that dose adjustment is necessary to avoid drug accumulation. However, a limitation of pharmacokinetic studies is the unclear relationship of antifactor Xa activity to thrombosis resolution or bleeding.<sup>18,19,34-37</sup> Thus, the practice of monitoring antifactor Xa activity to adjust doses has not been widely adopted. The results of our study combined with those cited in the first section of this paragraph suggest the potential usefulness of measuring antifactor Xa activity in patients with moderate renal function to assess anticoagulant accumulation and further stratify bleeding risk.

In an effort to bridge the gap between pharmacokinetic data and pharmacodynamic outcomes (bleeding), Barras et al<sup>38</sup> studied a model to quantify the probability of bleeding based on enoxaparin "exposure." They determined that bleeding as a function of total enoxaparin exposure was best described as the cumulative area under the concentration-time curve of antifactor Xa activity. Consequently, this analysis entails not only antifactor Xa activity at one point but also duration of therapy. Notably, the early major trials studied durations of therapy on average of only 4 days, which is markedly less exposure than in our study. The findings of Barras et al are important because they determined that cumulative exposure to anticoagulant levels over time was more directly related to bleeding than were antifactor Xa levels. Thorevska et al<sup>10</sup> also showed duration of therapy of significance for occurrence of bleeding. We did not measure antifactor Xa; however, our study used recommended therapeutic doses in patients with moderate renal impairment that pharmacokinetic studies have consistently shown to provide elevated antifactor Xa activity. Our results support the concept that increased exposure to enoxaparin via duration of therapy and possibly antifactor Xa accumulation is correlated with increased bleeding (**Table 4**). Studies of shorter duration would be less apt to discover bleeding or correlation of an antifactor Xa level determined early in therapy to predict bleeding.

When our results are added to previous evidence and the pharmacokinetics of enoxaparin, we believe that there are ample data confirming enoxaparin accumulation and an increased risk of major bleeding in patients with moderate renal impairment. Considering the impact of major bleeding as an adverse drug event that may include life-threatening or fatal hemorrhage, we suggest that regulatory agencies, the manufacturer, and/or guideline-writing organizations explore all available data, published and unpublished, and consider revising dosing and/or monitoring guidelines in patients with moderate renal impairment. Others<sup>7,15,17</sup> have offered alternative dosing strategies and, although use has been investigated in a limited number of patients, these regimens merit consideration (**Table 5**).

Limitations of this study include the retrospective data collection, therefore relying only on evaluation of clinical progress notes, laboratory test results, and other documentation. Our patient population consisted predominately of

**Table 4. Characteristics of Patients With Major Bleeding vs Those Without Major Bleeding**

Characteristic	Mean		P Value
	Major Bleeding (n = 19)	No Major Bleeding (n = 145)	
Length of enoxaparin sodium therapy, d	18.0	11.7	.03
Age, y	70.3	65.9	.14
Female sex, % <sup>a</sup>	40.0	60.0	.04
Weight, kg	85.7	94.8	.08
SCr level, mg/dL	1.3	1.0	.003
CrCl, mL/min <sup>b</sup>	57.5	85.3	.002
Platelet count, <100 × 10 <sup>9</sup> /μL	18.8	2.8	.008
Baseline INR	2.18	1.62	.006
Highest INR during enoxaparin therapy	2.64	2.74	.76
Concomitant therapy, %			
Aspirin	78.9	51.7	.02
Clopidogrel bisulfate <sup>b</sup>	5.3	9.7	.53
Warfarin	89.5	89.7	.98
Total No. of bleeding risk factors	1.4	1.5	.99

Abbreviations: CrCl, creatinine clearance; INR, international normalized ratio; SCr, serum creatinine.

SI conversion factors: To convert CrCl to milliliters per second, multiply by 0.0167; SCr to micromoles per liter, multiply by 88.4; and platelet count to × 10<sup>9</sup>/L, multiply by 1.

<sup>a</sup>Total of 5 women; 2 with major bleeding episodes.

<sup>b</sup>As estimated from the Cockcroft-Gault equation using lean body weight.

men and reflects patient selection from a population representative of a VA medical center. The decision to use enoxaparin vs other anticoagulants was not controlled, and bias may have been introduced without the proper randomization associated with prospective clinical trials. There also may be some residual confounding despite our efforts to control for differences in risk factors via multivariable regression. Several bleeding episodes followed cardiac ablation procedures (Table 3). It is possible that these bleeding events could have been avoided by using reduced doses of enoxaparin as recommended by some<sup>39</sup> or continuation of warfarin without bridging therapy as suggested by others.<sup>40,41</sup> The frequency of bleeding remained high even if these procedures were excluded. Despite these limitations, the comparative groups were similar in many demographics, including concurrent risk factors for bleeding. The demographics associated with reduced renal function (age, serum creatinine) differed as expected. It has been shown<sup>10</sup> that patients with reduced renal function may be at higher risk for bleeding with unfractionated heparin therapy as well as enoxaparin therapy; therefore, renal impairment itself and/or comorbidities associated with chronic kidney disease may contribute to increased bleeding. Even if this has an effect on risk separate from our concerns of drug accumulation, a dose adjustment to offset this risk should be investigated.

In conclusion, our results indicate a significantly increased risk of major bleeding in patients with moderate renal impairment who receive the recommended therapeutic dose of enoxaparin. This caution includes using

**Table 5. Published Alternative Enoxaparin Sodium Dosage Recommendations for Moderate Renal Impairment**

Source	Loading Dosage	CrCl, mL/min	Maintenance Dosage
Green et al, <sup>7</sup> 2005	1 mg/kg every 12 h (4 doses)	30-39 40-49	0.5 mg/kg every 12 h 0.6 mg/kg every 12 h
Hulot et al, <sup>15</sup> 2005	1 mg/kg (1 dose)	30-50	0.8 mg/kg every 12 h
Kruse and Lee, <sup>17</sup> 2004	1 mg/kg (1 dose)	30-60	0.75 mg/kg every 12 h

Abbreviation: CrCl, creatinine clearance.

SI conversion factor: To convert CrCl to milliliters per second, multiply by 0.0167.

these doses for bridge therapy. Further investigation of alternative dosing regimens in patients with moderate renal impairment to maintain efficacy with reduced risks in this patient population is warranted, as are studies of the role of monitoring antifactor Xa activity to guide dosing of enoxaparin.

Accepted for Publication: July 26, 2012.

Published Online: November 5, 2012. doi:10.1001/2013.jamainternmed.369

Correspondence: Douglas D. DeCarolis, PharmD, Pharmacy Service (119), Minneapolis Veterans Affairs Health Care System, One Veterans Drive, Minneapolis, MN 55417 (douglas.decarolis@va.gov).

Author Contributions: Dr DeCarolis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* DeCarolis, Thorson, Clairmont, and Johnson. *Acquisition of data:* DeCarolis, Thorson, Clairmont, and Leuthner. *Analysis and interpretation of data:* DeCarolis, Thorson, Clairmont, and Rector. *Drafting of the manuscript:* DeCarolis, Thorson, and Johnson. *Critical revision of the manuscript for important intellectual content:* DeCarolis, Thorson, Clairmont, Leuthner, and Rector. *Statistical analysis:* Rector. *Administrative, technical, and material support:* DeCarolis. *Study supervision:* DeCarolis and Johnson.

Conflict of Interest Disclosures: None reported.

## REFERENCES

- Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI; American College of Chest Physicians. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008; 133(6)(suppl):141S-159S.
- Lovenox [prescribing information]. <http://products.sanofi.us/lovenox/lovenox.html>. Accessed September 29, 2011.
- Hulot JS, Vantelon C, Urien S, et al. Effect of renal function on the pharmacokinetics of enoxaparin and consequences on dose adjustment. *Ther Drug Monit*. 2004;26(3):305-310.
- 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*. 2003;43(6):586-590.
- Becker RC, Spencer FA, Gibson M, et al; TIMI 11A Investigators. 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*. 2002;143(5):753-759.
- Bazinet A, Almanric K, Brunet C, et al. Dosage of enoxaparin among obese and renal impairment patients. *Thromb Res*. 2005;116(1):41-50.

7. 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*. 2005;59(3):281-290.
8. Sanderink GJ, Guimart CG, Ozoux ML, Jariwala NU, Shukla UA, Boutouyrie BX. Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment. *Thromb Res*. 2002;105(3):225-231.
9. Bruno R, Baille P, Retout S, et al. Population pharmacokinetics and pharmacodynamics of enoxaparin in unstable angina and non-ST-segment elevation myocardial infarction. *Br J Clin Pharmacol*. 2003;56(4):407-414.
10. Thorevska N, Amoteng-Adjepong Y, Sabahi R, et al. Anticoagulation in hospitalized patients with renal insufficiency: a comparison of bleeding rates with unfractionated heparin vs enoxaparin. *Chest*. 2004;125(3):856-863.
11. Gerlach AT, Pickworth KK, Seth SK, Tanna SB, Barnes JF. Enoxaparin and bleeding complications: a review in patients with and without renal insufficiency. *Pharmacotherapy*. 2000;20(7):771-775.
12. Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. *Clin Pharmacol Ther*. 2008;83(6):882-888.
13. Cestac P, Bagheri H, Lapeyre-Mestre M, et al. Utilisation and safety of low molecular weight heparins: prospective observational study in medical inpatients. *Drug Saf*. 2003;26(3):197-207.
14. Fox KA, Antman EM, Montalescot G, et al. The impact of renal dysfunction on outcomes in the EXTRACT-TIMI 25 trial. *J Am Coll Cardiol*. 2007;49(23):2249-2255.
15. Hulot JS, Montalescot G, Lechat P, Collet JP, Ankri A, Urien S. Dosing strategy in patients with renal failure receiving enoxaparin for the treatment of non-ST-segment elevation acute coronary syndrome. *Clin Pharmacol Ther*. 2005;77(6):542-552.
16. Barras MA, Duffull SB, Atherton JJ, Green B. Individualized dosing of enoxaparin for subjects with renal impairment is superior to conventional dosing at achieving therapeutic concentrations. *Ther Drug Monit*. 2010;32(4):482-488.
17. Kruse MW, Lee JJ. Retrospective evaluation of a pharmacokinetic program for adjusting enoxaparin in renal impairment. *Am Heart J*. 2004;148(4):582-589.
18. Hammerstingl C. Monitoring therapeutic anticoagulation with LMWHs: is it useful or misleading? *Cardiovasc Hematol Agents Med Chem*. 2008;6:282-286.
19. Barrowcliffe TW. Laboratory monitoring of low-molecular-weight heparin therapy—part II. *J Thromb Haemost*. 2005;3(3):575-576.
20. Janmahasatian S, Duffull SB, Chagnac A, Kirkpatrick CMJ, Green B. Lean body mass normalizes the effect of obesity on renal function. *Br J Clin Pharmacol*. 2008;65(6):964-965.
21. Pesola GR, Akhavan I, Madu A, Shah NK, Carlon GC. Prediction equation estimates of creatinine clearance in the intensive care unit. *Intensive Care Med*. 1993;19(1):39-43.
22. Schulman S, Beyth RJ, Kearon C, Levine MN; American College of Chest Physicians. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). *Chest*. 2008;133(6)(suppl):257S-298S.
23. Nieuwenhuis HK, Albada J, Banga JD, Sixma JJ. Identification of risk factors for bleeding during treatment of acute venous thromboembolism with heparin or low molecular weight heparin. *Blood*. 1991;78(9):2337-2343.
24. Cohen M, Demers C, Gurfinkel E, et al; Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med*. 1997;337:447-452.
25. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med*. 1996;334:677-681.
26. Merli G, Spiro T, Olsson C, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med*. 2001;134:191-202.
27. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. *N Engl J Med*. 1998;338(7):409-415.
28. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593-1601.
29. Blazing MA, de Lemos JA, White HD, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. *JAMA*. 2004;292:55-64.
30. Cohen M, Thérout P, Borzak S, et al. Randomized double-blind safety study of enoxaparin versus unfractionated heparin in patients with non-ST-segment elevation acute coronary syndromes treated with tirofiban and aspirin: the ACUTE II study. *Am Heart J*. 2002;144:470-477.
31. Antman EM, Morrow DA, McCabe CH, et al; EXTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477-1488.
32. Fox KA, Bassand JP, Mehta SR, et al; OASIS 5 Investigators. 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(5):304-310.
33. Collet JP, Montalescot G, Fine E, et al. Enoxaparin in unstable angina patients who would have been excluded from randomized pivotal trials. *J Am Coll Cardiol*. 2003;41(1):8-14.
34. Bounameaux H, de Moerloose P. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? no. *J Thromb Haemost*. 2004;2(4):551-554.
35. Harenberg J. Is laboratory monitoring of low-molecular-weight heparin therapy necessary? yes. *J Thromb Haemost*. 2004;2(4):547-550.
36. Boneu B. Laboratory monitoring of low-molecular-weight heparin therapy—part II. *J Thromb Haemost*. 2005;3(3):573-574.
37. Hemker HC, Al Dieri R, Béguin S. Laboratory monitoring of low-molecular-weight heparin therapy—part II: monitoring LMWH therapy? for the moment a non-question. *J Thromb Haemost*. 2005;3:571-573.
38. Barras MA, Duffull SB, Atherton JJ, Green B. Modelling the occurrence and severity of enoxaparin-induced bleeding and bruising events. *Br J Clin Pharmacol*. 2009;68(5):700-711.
39. European Heart Rhythm Association (EHRA); European Cardiac Arrhythmia Society (ECAS); American College of Cardiology (ACC); American Heart Association (AHA); Society of Thoracic Surgeons (STS), Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up: a report of the Heart Rhythm Society (HRS) Task Force on Catheter and Surgical Ablation of Atrial Fibrillation [published correction appears in *Heart Rhythm*. 2009;6(1):148]. *Heart Rhythm*. 2007;4(6):816-861.
40. Ahmed I, Gertner E, Nelson WB, et al. Continuing warfarin therapy is superior to interrupting warfarin with or without bridging anticoagulation therapy in patients undergoing pacemaker and defibrillator implantation. *Heart Rhythm*. 2010;7(6):745-749.
41. Di Biase L, Burkhardt JD, Mohanty P, et al. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation: the impact of periprocedural therapeutic international normalized ratio. *Circulation*. 2010;121(23):2550-2556.

## INVITED COMMENTARY

# Moderate Renal Impairment and Risk of Bleeding With Anticoagulation

**B**leeding is the most feared complication of anticoagulant therapy and, unfortunately, it is not uncommon. The 2011-2012 National Patient Safety Goals mandate efforts to “reduce the likelihood of pa-

tient harm associated with the use of anticoagulant therapy.”<sup>1</sup> This is a call for coordinated efforts to decrease adverse events related to anticoagulant therapy, with recommendations for improved oversight and evi-