Anticoagulation in Hospitalized Patients With Renal Insufficiency*

A Comparison of Bleeding Rates With Unfractionated Heparin vs Enoxaparin

Natalya Thorevska, MD; Yaw Amoateng-Adjepong, MD, MPH, PhD; Ramin Sabahi, MD; Irina Schiopescu, MD; Anan Salloum, MD; Visvanathan Muralidharan, MD; and Constantine A. Manthous, MD, FCCP

Objectives: To compare the rates of bleeding complications in patients with renal insufficiency who receive anticoagulation therapy with the full therapeutic dose, unfractionated heparin (UFH), or with twice-daily enoxaparin.

Setting: A 325-bed community teaching hospital.

Study type: Retrospective cohort study.

Methods: The medical records of all patients with renal insufficiency who received anticoagulation therapy with UFH or enoxaparin during a 13-month period were reviewed for the occurrence of major and minor bleeding. Incidence rates were computed per 1,000-person days of anticoagulation therapy. Comparisons were made across categories of renal insufficiency and other potential confounders.

Results: A total of 620 patients with estimated glomerular filtration rates of <60 mL/min were studied. Of these, 331 received anticoagulation therapy with UFH, 250 with enoxaparin, and 39 with both (not simultaneously). The major bleeding rates were 26.3 per 1,000 person-days for UFH and 20.7 per 1,000 person-days for enoxaparin. Major bleeding complications were similarly increased for both UFH and enoxaparin therapy across categories of worsening renal insufficiency. Patients with severe renal insufficiency while receiving enoxaparin had a 154% excess incidence of minor bleeding compared to those receiving UFH (incidence ratio, 2.54; 95% confidence interval, 1.01 to 6.36). Worsening renal insufficiency, female gender, and prolonged duration of anticoagulation therapy emerged as the main determinants for bleeding complications.

Conclusion: Both the twice-daily enoxaparin and UFH regimens are associated with comparable increases in major bleeding complications in patients with renal dysfunction receiving full-dose anticoagulation therapy. Both agents should be used with caution in anticoagulation therapy for patients with renal insufficiency. (CHEST 2004; 125:856–863)

Key words: anticoagulation; bleeding; enoxaparin; hemorrhage; heparin; renal insufficiency

Abbreviations: APTT = activated partial thromboplastin time; CI = confidence interval; GFR = glomerular filtration rate; IDR = incidence density ratio; RR = risk ratio; UFH = unfractionated heparin

The ease of use and clinical efficacy of enoxaparin have led to its widespread use for anticoagulation therapy in a number of disorders.1–5 Enoxaparin is entirely excreted by the kidneys, and, accordingly, in the absence of data regarding safety, the manufacturer has warned against its use in patients with renal insufficiency. Despite these warnings, enoxaparin has been used in anticoagulation therapy for patients with varying degrees of renal insufficiency in many hospitals. Cases of bleeding complications in patients with renal insufficiency have been reported.6,7 To date, there is no clear quantification of the degree of risk of bleeding during treatment with enoxaparin and whether the risk is higher than anticoagulation therapy with unfractionated heparin (UFH). This retrospective cohort study was undertaken to compare bleeding rates in patients with renal insuffi-
Diet in Renal Disease Study Group equation. Computerized 
tained by our pharmacy unit. The glomerular filtration rates 
comprised of dispensed medications that is main-
2000, through June 30, 2001, at our hospital was obtained from a 
2000, through June 30, 2001, at our hospital was obtained from a 
data acquisition sheet. The abstracted data included patient 
demographics, weight, date of hospital admission, indications for 
anticoagulation therapy, anticoagulant type/dose, duration of 
anticoagulation therapy, platelet count, coadministration of med-
ications that might affect bleeding tendency, and disposition from 
the hospital (ie, discharged from the hospital alive or dead). 
Data regarding bleeding complications and any blood or plasma 
transfusions administered during the days of therapy with either 
UFH or enoxaparin were collected. Patients who received only 
prophylactic doses of either enoxaparin or UFH were excluded. 
UFH was administered by continuous IV infusion after an initial 
bolus. Dosages and titration rates were based on a weight-based 
normogram. The activated partial thromboplastin time (APTT) 
was monitored for all patients before and after 4 h of initiation of 
UFH therapy. Adjustments in the titration rates and the fre-
cency of further APTT determinations were guided by a 
standardized protocol (available on request). The dose of enoxa-
aparin was 1 mg/kg body weight administered subcutaneously 
twice a day. Doses were not adjusted based on the degree of renal 
insufficiency. Also, enoxaparin levels using an anti-factor Xa-
based assay were not monitored.

Data Analysis

For purposes of analyses, all patients were categorized into 
groups with mild renal insufficiency (estimated GFR, 41 to 60 
ml/min), moderate renal insufficiency (estimated GFR, 21 to 40 
ml/min), or severe renal insufficiency (estimated GFR, ≤ 20 ml/min). Bleeding complications were classified as 
being major or minor according to previously described 
criteria. Major bleeding was defined as bleeding resulting in a 
hemoglobin drop of ≥ 3 g/dL, the requirement of two or 
more units of packed RBCs given within 48 hours or intraoc-
ular, retroperitoneal, or intracranial hemorrhage. All other 
bleeding episodes, including overt GI bleeding without a 
decrease in hemoglobin of ≥ 3 g/dL, were classified as minor 
bleeds. Each bleeding complication was assigned to the type of 
anticoagulation therapy that the patient was receiving at the 
time of the bleeding episode. The duration of anticoagulation 
therapy was calculated in days. Bleeding incidence rate for 
each type of anticoagulation therapy was calculated as new 
episodes of bleeding per 1,000 person-days of anticoagulant 
therapy. For patients receiving anticoagulation therapy with 
both agents, the duration of therapy with each agent was 
individually computed. Also, bleeding complications were 
assigned to the specific anticoagulant that the patient’s condi-
tion was being managed with at the time of the bleeding event. 
Incidence density ratios (IDRs) and risk ratios (RRs) were 
computed where appropriate. Comparisons were made across 
categories of renal insufficiency, between bleeders and nonbleed-
ers, and between decedents and those patients discharged from 
the hospital alive. Predictors of bleeding complications were 
ascertained using stratified analysis, Cox proportional hazards 
analysis, and logistic regression analysis. A p value of < 0.05 was 
used to signify statistical significance.

To adjust for potential selection bias in the nonrandomized 
choice of UFH or enoxaparin by individual physicians for their 
patients, propensity score analyses were performed. In general, 
the propensity score is the chance of receiving one treatment 
compared to another with given observed prognostic variables. 
The propensity scores were estimated using logistic regression 
analyses with assignment to enoxaparin as the outcome of 
interest, and the potential indicators for anticoagulation, gender, 
estimated GFR, comorbid conditions, and concurrent medica-
tions as the predictor variables. Patients were categorized into 
empiric quartiles on the basis of their individual propensity 
scores. The Cox proportional hazards regression and logistic 
regression analyses (for determinants of major bleeding) were 
performed using the propensity score groups as covariates in the 
regression model or by using the propensity scores as a stratifying 
variable. 

Overall, the criteria for variable inclusion in the various 
regression models were based on biological plausibility, current 
clinical practice, and evidence of association in the univariate 
analysis. The backward elimination approach was used in arriving 
at the final main-effects models. Effect modification and 
confounding were assessed using standard methods. Summary mea-
sures of goodness of fit were evaluated.

Results

A total of 620 distinct hospitalizations fulfilled our 
inclusion criteria. Of these, 331 patients (53.4%) 
received anticoagulation therapy with UFH, 250 
patients (40.3%) with enoxaparin, and 39 (6.3%) with 
both UFH and enoxaparin (not simultaneously) 
during the same hospitalization. The patients were 
predominantly white (81.6%) and elderly (83.7% 
were > 65 years of age) [Table 1]. The median age 
was 80 years. Half of the cohort (50.2%) had mild 
renal insufficiency, 34% had moderate renal insuffi-
ciency, and 15.8% had severe renal insufficiency. Of 
those with severe renal insufficiency, 35 were receiv-
ing hemodialysis and 3 were receiving peritoneal 
dialysis. The median estimated GFR was 40.1 mL/
min for the entire cohort (interquartile range, 26.4 to 
50.9 mL/min).

When stratified by the type of anticoagulant used, 
the patients did not differ by gender, race/ethnicity, 
age, or severity of renal insufficiency (Table 1). 
Overall, patients receiving both UFH and enoxapa-
rin had longer durations of anticoagulation therapy (53.8% of all patients received therapy for \( >7 \) days; 85% of patients receiving UFH only received therapy for \( >7 \) days). Overall, there was a total of 2,537 person-days of anticoagu-

### Table 1—Selected Cohort Characteristics and Outcomes Stratified by Type of Anticoagulant Used During the Course of Hospitalization*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Cohort</th>
<th>UFH Only</th>
<th>Enoxaparin Only</th>
<th>Both UFH and LMWH</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. %</strong></td>
<td>620</td>
<td>331</td>
<td>250</td>
<td>39</td>
<td>100</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>291</td>
<td>153</td>
<td>126</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>Female</td>
<td>329</td>
<td>178</td>
<td>124</td>
<td>27</td>
<td>69.2</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>506</td>
<td>265</td>
<td>204</td>
<td>37</td>
<td>94.9</td>
</tr>
<tr>
<td>Non-white</td>
<td>114</td>
<td>66</td>
<td>46</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>Age, yr</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;65 )</td>
<td>101</td>
<td>61</td>
<td>35</td>
<td>5</td>
<td>12.8</td>
</tr>
<tr>
<td>( 65-74 )</td>
<td>146</td>
<td>80</td>
<td>54</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>( \geq 75 )</td>
<td>373</td>
<td>190</td>
<td>161</td>
<td>22</td>
<td>56.4</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>77</td>
<td>76</td>
<td>78</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>GFR, mL/min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( 41-60 )</td>
<td>311</td>
<td>171</td>
<td>122</td>
<td>18</td>
<td>46.2</td>
</tr>
<tr>
<td>( 21-40 )</td>
<td>211</td>
<td>100</td>
<td>95</td>
<td>16</td>
<td>41.0</td>
</tr>
<tr>
<td>( \geq 20 )</td>
<td>98</td>
<td>60</td>
<td>33</td>
<td>5</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>40.1</td>
<td>41.3</td>
<td>39.3</td>
<td>37.2</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Serum creatinine, mg/dL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( &lt;1.2 )</td>
<td>152</td>
<td>85</td>
<td>55</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>( 1.2-1.4 )</td>
<td>176</td>
<td>87</td>
<td>78</td>
<td>11</td>
<td>28.2</td>
</tr>
<tr>
<td>( 1.5-2.4 )</td>
<td>182</td>
<td>96</td>
<td>76</td>
<td>10</td>
<td>25.6</td>
</tr>
<tr>
<td>( \geq 2.5 )</td>
<td>110</td>
<td>63</td>
<td>41</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Anticoagulation days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>267</td>
<td>157</td>
<td>110</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>3-7</td>
<td>280</td>
<td>146</td>
<td>116</td>
<td>18</td>
<td>46.2</td>
</tr>
<tr>
<td>( &gt;7 )</td>
<td>73</td>
<td>28</td>
<td>24</td>
<td>21</td>
<td>53.8</td>
</tr>
<tr>
<td><strong>Mean \pm SE</strong></td>
<td>0.8-2.36</td>
<td>0.5-23.6</td>
<td>0.9-12.6</td>
<td>0.9-6.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>300</td>
<td>103</td>
<td>83</td>
<td>14</td>
<td>35.9</td>
</tr>
<tr>
<td>ACS</td>
<td>331</td>
<td>161</td>
<td>147</td>
<td>23</td>
<td>59.0</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>113</td>
<td>66</td>
<td>40</td>
<td>7</td>
<td>17.9</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>22</td>
<td>17</td>
<td>3</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td>All others</td>
<td>70</td>
<td>45</td>
<td>19</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumadin</td>
<td>151</td>
<td>80</td>
<td>50</td>
<td>12</td>
<td>30.8</td>
</tr>
<tr>
<td>Aspirin</td>
<td>335</td>
<td>171</td>
<td>147</td>
<td>20</td>
<td>51.3</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>104</td>
<td>67</td>
<td>29</td>
<td>8</td>
<td>20.5</td>
</tr>
<tr>
<td>Glycoprotein HB/IIIA</td>
<td>38</td>
<td>28</td>
<td>4</td>
<td>6</td>
<td>15.4</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>75</td>
<td>55</td>
<td>19</td>
<td>48.7</td>
</tr>
<tr>
<td>Major</td>
<td>60</td>
<td>30</td>
<td>22</td>
<td>8</td>
<td>20.5</td>
</tr>
<tr>
<td>Minor</td>
<td>89</td>
<td>45</td>
<td>33</td>
<td>11</td>
<td>28.2</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>68</td>
<td>38</td>
<td>23</td>
<td>7</td>
<td>17.9</td>
</tr>
</tbody>
</table>

*LMWH = low-molecular-weight heparin; DVT = deep vein thrombosis; PE = pulmonary embolism; ACS = acute coronary syndrome.*
lulation therapy (enoxaparin therapy, 1,206 person-days; UFH therapy, 1,331 person-days).

The major indications for anticoagulation therapy were acute coronary syndrome (331 patients; 53.4%), atrial fibrillation (200 patients; 32.3%), deep vein thrombosis with or without pulmonary embolism (113 patients; 18.2%), ischemic stroke (22 patients; 3.5%), and others, including cardiomyopathies with low ejection fractions (70 patients; 11.3%). One hundred ten patients (17.7%) had more than one indication for anticoagulation therapy. Patients receiving aspirin, 151 patients (24.4%) were receiving other antiplatelet medications. One hundred thirty-five patients (54.0%) were receiving warfarin, 104 patients (16.8%) were receiving enoxaparin and UFH were excluded from the analysis when patients who received both (sequential) enoxaparin and UFH were included in the analysis (summary IDR, 0.8; 95% CI, 0.4 to 1.3).

In addition to the use of UFH or enoxaparin, 484 patients (78.1%) received other antithrombotic agents. Three hundred thirty-five patients (54.0%) were receiving aspirin, 151 patients (24.4%) were receiving warfarin, 104 patients (16.8%) were receiving clopidogrel, and 51 patients (8.2%) were receiving other antiplatelet medications. One hundred twenty-one patients (19.5%) were given two or more antithrombotic agents. Patients receiving enoxaparin were less likely to be given clopidogrel or agents inhibiting platelet glycoprotein IIb/IIIa function. There was a total of 149 bleeding complications among 125 (of the 620) hospital admissions. Sixty of these (40.2%) were major bleeding and 89 (59.7%) were minor bleeding episodes. The GI tract was the most common site of major bleeding (47%). Table 2 and Figure 1 show the incidence and IDRs of major and minor bleeding across categories of renal insufficiency, respectively. Overall, the frequency of bleeding increased with worsening renal insufficiency, irrespective of the agent used. Among patients with mild or moderate renal insufficiency, the observed incidence rates of major bleeding appeared to be greater for patients receiving anticoagulation therapy with UFH compared with those receiving therapy with enoxaparin. This trend was reversed in patients with severe renal insufficiency. However, none of these differences achieved statistical significance (summary IDR, 0.7; 95% CI, 0.4 to 1.2; mild renal insufficiency IDR, 0.7; 95% CI, 0.3 to 2.0; moderate renal insufficiency IDR, 0.5; 95% CI, 0.3 to 1.1; severe renal insufficiency IDR, 1.2; 95% CI, 0.4 to 3.3). Among the subgroup of patients with severe renal insufficiency, there was a significantly higher rate of minor bleeding in those treated with enoxaparin vs those treated with UFH (IDR, 2.5; 95% CI, 1.01 to 6.36). Similar results were obtained when patients who received both (sequential) enoxaparin and UFH were excluded from the analysis (summary IDR, 0.8; 95% CI, 0.4 to 1.3).

Table 2—Bleeding Incidence Rates per 1,000 Person-Days of Anticoagulation Therapy and IDRs, Comparing Patients Receiving Enoxaparin with Those Receiving UFH, Stratified by Degree of Renal Insufficiency (Based on Estimated GFR) and Type of Anticoagulant Used

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate</td>
<td>95% CI</td>
<td>Rate</td>
<td>95% CI</td>
</tr>
<tr>
<td>Type of bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>26.3</td>
<td>17.6–35.0</td>
<td>16.9</td>
<td>7.3–26.4</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>20.7</td>
<td>12.6–28.9</td>
<td>12.4</td>
<td>2.5–22.4</td>
</tr>
<tr>
<td>Total</td>
<td>23.7</td>
<td>17.7–29.6</td>
<td>15.1</td>
<td>8.1–22.1</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>39.1</td>
<td>28.5–49.7</td>
<td>39.3</td>
<td>24.8–54.0</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>32.3</td>
<td>22.2–42.5</td>
<td>24.9</td>
<td>10.8–39.0</td>
</tr>
<tr>
<td>Total</td>
<td>35.1</td>
<td>27.9–42.4</td>
<td>33.5</td>
<td>23.1–43.9</td>
</tr>
<tr>
<td>Ever bled (major or minor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>55.6</td>
<td>42.9–68.2</td>
<td>46.4</td>
<td>30.6–62.2</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>44.8</td>
<td>32.8–56.7</td>
<td>35.3</td>
<td>18.5–52.0</td>
</tr>
<tr>
<td>Total</td>
<td>49.3</td>
<td>40.6–57.9</td>
<td>41.1</td>
<td>30.1–52.6</td>
</tr>
<tr>
<td>All (major and minor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>65.4</td>
<td>51.6–79.1</td>
<td>56.3</td>
<td>38.9–73.7</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>53.1</td>
<td>40.1–66.1</td>
<td>37.3</td>
<td>20.1–54.6</td>
</tr>
<tr>
<td>Total</td>
<td>58.8</td>
<td>50.0–69.0</td>
<td>48.6</td>
<td>36.1–61.1</td>
</tr>
<tr>
<td>IDRs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeds</td>
<td>0.79</td>
<td>0.47–1.32</td>
<td>0.73</td>
<td>0.28–1.97</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>0.53</td>
<td>0.35–1.25</td>
<td>0.63</td>
<td>0.32–1.24</td>
</tr>
<tr>
<td>Ever bled</td>
<td>0.81</td>
<td>0.57–1.14</td>
<td>0.76</td>
<td>0.42–1.36</td>
</tr>
<tr>
<td>All bleeds</td>
<td>0.81</td>
<td>0.59–1.11</td>
<td>0.66</td>
<td>0.39–1.14</td>
</tr>
</tbody>
</table>
Table 3 shows selected characteristics of patients with and without major bleeding. Worsening renal insufficiency and female gender emerged as the independent predictors of major bleeding complications in the multivariate analyses. Patients with serum creatinine concentrations of $\geq 1.5$ mg/dL had an absolute increase of 13.4 episodes of major bleeding per 1,000 person-days of anticoagulation therapy (adjusted hazards ratio, 1.3; 95% CI, 1.0 to 1.6; adjusted RR, 1.5; 95% CI, 1.1 to 2.9). Similarly, female patients had an absolute increase of 7.6 episodes of major bleeding per 1,000 person-days of anticoagulation therapy compared to men (adjusted hazards ratio, 1.3; 95% CI, 1.1 to 1.5; $p = 0.009$; adjusted RR, 1.8; 95% CI, 1.1 to 3.0). Similar hazard ratios were observed after adjusting for the propensity scores.

Patients receiving anticoagulation therapy for $> 3$ days experienced a 150% excess risk of major bleeding compared to patients receiving anticoagulation therapy for between 1 and 3 days (adjusted RR, 3.0; 95% CI, 1.8 to 5.0). However, expressed per number of days of anticoagulation therapy, the incidence rate was slightly lower in the group receiving prolonged anticoagulation therapy (ie, 22.0 vs 28.3 per 1,000 person-days; IDR, 0.8; 95% CI, 0.5 to 1.3). The duration of anticoagulation therapy was of exceptional significance for the occurrence of bleeding in the subgroup of patients treated with enoxaparin. Whereas only 3.1% of patients receiving anticoagulation therapy between 1 and 3 days had a major bleed, 15.5% of those treated for $> 3$ days had bleeding (RR, 5.0; 95% CI, 1.9 to 12.9). For those treated with heparin, 48.6% of major bleeding and 65.3% of minor bleeding occurred in the first 3 days of anticoagulation therapy.

Twenty-four percent of heparin-related major bleeding were temporally related to an APTT $> 85$ s. There was no association between the specific indication for anticoagulation therapy and the occurrence of a major or minor bleed. Similarly, the type or number of additional antithrombotic agents that a patient received was not associated with bleeding occurrence.

There were 68 deaths (11.0%) in the whole cohort. There was a strong association between the degree of renal insufficiency and in-hospital, all-cause mortality ($p < 0.0001$). Also, there was a strong association between the occurrence of a major bleeding complication and all-cause mortality, even after excluding deaths that were probably attributable to bleeding ($p < 0.0001$). There was no association between gender, race/ethnicity, or age and the all-cause mortality.

**DISCUSSION**

Contrary to our expectations, there was no statistically significant difference in the incidence of major bleeding in patients “therapeutically anticoagulated” with twice-daily dosing of enoxaparin compared with dosing with UFH across all levels of renal insufficiency. Among patients with severe renal insufficiency, there was a 150% excess incidence of minor bleeding in the enoxaparin group. No similar excess was seen in the patients with mild or moderate renal insufficiency. Also, the data demonstrated an increase in the risk of bleeding with increasing severity of renal insufficiency, irrespective of the agent used.

UFH is rapidly metabolized by a saturable, zero-order mechanism, mainly by the reticuloendothelial...
pharmacokinetic parameters were similar in both compared to normal control subjects. All other Xa assay in patients with severe renal insufficiency heparin half-life based on the results of a anti-factor netic study demonstrated a twofold prolongation in clearance. Less than 10% is excreted in urine system. This is followed by a slower first-order renal clearance. The mean half-life is dependent on the administered dose and is unchanged with abnormal renal function. Exonaparin, on the other hand, is excreted mainly by the kidneys. In experimental animals, the biological half-life of exonaparin is increased with renal failure. The effect of renal function on the half-life of exonaparin in humans appears less certain. A single-dose pharmacokinetic study demonstrated a twofold prolongation in heparin half-life based on the results of a anti-factor Xa assay in patients with severe renal insufficiency compared to normal control subjects. All other pharmacokinetic parameters were similar in both groups of patients. These led the authors to conclude that “end stage renal disease has little effect on the pharmacokinetics of exonaparin, and dosing adjustments are unnecessary.” However, in another study, in which daily prophylactic doses of exonaparin were given for 4 days, the elimination half-life increased with the degree of renal impairment and was more evident after repeated dosing. The exonaparin clearance on day 4 was 39% lower in patients with severe renal impairment than in healthy volunteers. A decrease in the number of patients with mild or moderate renal insufficiency was not statistically significant.

There have been reports of excessive drug accumulation or bleeding complications in patients with renal insufficiency treated with the usual doses of exonaparin. Bleeding complications were noted in two patients with very mild renal insufficiency (creatinine clearance rate, 60 to 70 mL/min) who received anticoagulation therapy with exonaparin for several months. A retrospective review of the experience at one tertiary medical center revealed excess bleeding complications in patients with renal insufficiency compared with those with normal renal function. However, no comparative data were provided for patients receiving anticoagulation therapy with UFH. Finally, a recent review of the literature performed by Nagge and colleagues concluded the following: “The use of a 30-mL/min (0.50-mL/s) cutoff (for use of low molecular weight heparins) is not justified, on the basis of currently available evidence.”

To our knowledge, this is the first study the purpose of which was to compare bleeding rates in patients with renal insufficiency who received anticoagulation therapy with therapeutic doses of exonaparin or UFH. We had postulated excess bleeding incidence with exonaparin compared to UFH on the basis of the known differences in renal clearance. The comparable rates of bleeding complications with either agent at the same levels of renal insufficiency suggest that factors other than drug clearance play a role in the bleeding complications. It is probable that the unfavorable clearance of exonaparin in patients with renal insufficiency is offset by the decreased inhibition of platelet function and by less interference with platelet and vessel wall interaction compared to that of UFH. Renal failure by itself increases the risk of bleeding by impairing platelet adhesion and aggregation.

It is plausible that the lack of a statistically significant difference in the bleeding complications between the two groups is due, in part, to the relatively small sample sizes in each of the categories of renal insufficiency, and by a reversal of the trend in patients with severe renal insufficiency compared
with those with mild or moderate renal insufficiency. Whereas there was an almost 30 to 50% reduction in the bleeding rates for the enoxaparin group in patients with mild or moderate renal insufficiency, there was a 20% excess in major bleeding complications for the enoxaparin group in patients with severe renal insufficiency.

The observation of increased bleeding rates in women receiving anticoagulation therapy with heparin is not new.30–32 This female preponderance has been proven to be independent of body mass and appears to be related to alterations in the pharmacokinetics of heparin in women.30 Our study extends this observation to women receiving anticoagulation therapy with enoxaparin.

The study was limited by its retrospective cohort study design. Study subjects were not randomized to the type of anticoagulant used. Although modern statistical techniques, including propensity score analysis and multivariate modeling, were used to adjust for potential selection bias and confounding, residual (hidden) selection bias and confounding are still possible. The small numbers of intracranial bleeding and other site-specific major bleeding did not allow for a meaningful subgroup analysis using site-specific bleeding as the outcome of interest. Another important limitation of this study is that we did not ascertain the bleeding rates at variable doses of enoxaparin or with anti-factor Xa activity monitoring. Some have suggested23 that such monitoring may prove useful in identifying the likelihood of bleeding during anticoagulation therapy with enoxaparin. However, future studies are required to examine this hypothesis.

These limitations notwithstanding, the study demonstrates that the use of both UFH and enoxaparin are associated with similar increases in major bleeding complications in patients with renal insufficiency, and that unmonitored, full-dose enoxaparin therapy (administered as twice-daily dosing) is no less safe than monitored, full-dose UFH therapy in patients with renal insufficiency. Both agents should be used with caution in patients with renal insufficiency. Prospective studies are needed to clarify the role of anti-factor Xa activity monitoring and/or enoxaparin dose adjustment in patients with severe renal insufficiency.

ACKNOWLEDGMENT: The authors acknowledge the significant contributions of Pritee Gada, MD, in data gathering and editing.

REFERENCES
17 Eiber HB, Danishefsky I, Barrelli FJ. Studies with radioactive heparin in humans. Angiology 1960; 11:40–43
20 Palm M, Mattsson CH. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. Thromb Haemost 1987; 58:932–935
22 Sanderink GJ, Guimart CG, Ozoux ML, et al. Pharmacokinetics and pharmacodynamics of the prophylactic dose of

Governors Community Service Awards Program

Each year The CHEST Foundation confers awards to ACCP members for pro bono service in chest and critical care medicine. Saluting volunteer service worldwide, this program recognizes ACCP members who donate their time and medical expertise and confers 22 monetary awards totalling $140,000 to the organizations where they volunteer. Awards are determined through a competitive peer-reviewed process.

Application deadline: May 14, 2004

Applications for all awards are being accepted now. Apply Today!

Access more details for most awards at www.chestfoundation.org, or contact Sue Ciezadlo at sciezadlo@chestnet.org or 847-498-8363.

For the scientific abstract-related awards only, access details at www.chestnet.org