Excess Dosing of Antiplatelet and Antithrombin Agents in the Treatment of Non–ST-Segment Elevation Acute Coronary Syndromes

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Current Quality Improvement efforts in acute cardiovascular care are focused on closing treatment gaps so more eligible patients receive evidence-based therapies.1,2 Beyond ensuring that effective therapies are administered, attention should also be directed at ensuring these therapies are given both correctly and safely. In acute coronary syndromes (ACS), early use of antiplatelet and antithrombin therapy plays a key role in altering the thrombotic process resulting from plaque rupture, thereby improving patient outcomes.3-10 Numerous studies have also helped define dosing strategies for antithrombotic therapy; these individualized dosing strategies based on weight and renal function minimize bleeding risk while preserving therapeutic benefits.11-19 Despite these guidelines, bleeding complications remain a major concern in patients with non–ST-segment

Context Effective medical care assumes delivery of evidence-based medicines to appropriate patients with doses comparable to those studied.

Objective To investigate dosing of unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and glycoprotein IIb/IIIa inhibitors, and the association between dosing and major outcomes.

Design, Setting, and Participants A prospective observational analysis in 387 US academic and nonacademic hospitals of 30 136 patients from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative Registry who had non–ST-segment elevation acute coronary syndromes (NSTE ACS) with chest pain and either positive electrocardiograms or cardiac biomarkers between January 1 and September 30, 2004.

Main Outcome Measures Excessive dosing of UFH, LMWH, and glycoprotein IIb/IIIa inhibitors and major clinical outcomes, including bleeding, in-hospital mortality, and length of stay.

Results A total of 3354 patients (42%) with NSTE ACS who were administered antithrombotic agents received at least 1 initial dose outside the recommended range. An excess dose was administered to 2934 patients (32.8%) treated with UFH, 1378 (13.8%) treated with LMWH, and 2784 (26.8%) treated with glycoprotein IIb/IIIa inhibitors. Factors associated with excess dosing included older age, as well as female sex, renal insufficiency, low body weight, diabetes mellitus, and congestive heart failure. Relative to those patients not administered excess dosages, patients with excess dosages of UFH, LMWH, and glycoprotein IIb/IIIa inhibitors either tended toward or had higher risks for major bleeding (adjusted odds ratio [OR], 1.08; 95% confidence interval [CI], 0.94-1.26; OR, 1.39; 95% CI, 1.11-1.74; and OR, 1.36; 95% CI, 1.10-1.68; respectively). Bleeding increased relative to the degree of excess dose and to the number of agents administered in excess (6.6% [237/3590] if neither heparin nor glycoprotein IIb/IIIa excess vs 22.2% [93/419] if both excess). Mortality and length of stay were also higher among those patients administered excess dosing. We estimated that 15% (400/2766) of major bleeding in this population may be attributable to excess dosing.

Conclusions Patients with NSTE ACS treated in the community often receive excess doses of antithrombotic therapy. Dosing errors occur more often in vulnerable populations and predict an increased risk of major bleeding.

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elevation (NSTE) ACS and occur in approximately 3% to 9% of selected clinical trial populations; even higher rates have been reported in the community. 9,10,20,21 Antithrombotic agents have narrow therapeutic windows, which makes dosing an important concern. In addition, patient factors have been associated with greater risk of bleeding. However, the variation and impact of antithrombotic dosing on the safety of evidence-based medicine has yet to be carefully studied outside of the standardized clinical trial environment, or after adjusting for patient factors.

We describe dosing of antithrombotic therapies administered to patients with NSTE ACS in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative Registry. We sought to determine the frequency with which unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and glycoprotein IIb/IIIa inhibitors were administered in doses exceeding recommendations; patient and hospital factors associated with the delivery of excess doses; and the association between dosing and major outcomes after adjustment.

METHODS
CRUSADE Registry
The CRUSADE National Quality Improvement Initiative Registry is an ongoing database of high-risk patients with NSTE ACS admitted to US academic and nonacademic hospitals since November 2001. 22-24 Eligibility for the CRUSADE registry requires ischemic symptoms lasting at least 10 minutes combined with positive cardiac markers (troponin or creatinine kinase-MB) or ischemic ST-segment electrocardiograph changes (ST-segment depression or transient ST-segment elevation) within 24 hours of hospital admission. CRUSADE hospitals are diverse in size, teaching status, capacity, and region. Relative to national averages, CRUSADE hospitals are larger and more likely to have catheterization laboratories and cardiac surgical capabilities. Participating hospitals collect data through retrospective chart review by using standardized data collection tools. 25 Data elements include baseline demographics, clinical presentation, comorbidities, use of medications within the first 24 hours of hospitalization, use and timing of invasive cardiac procedures, laboratory results, physician and hospital characteristics, interventions, and in-hospital outcomes. The institutional review board of each hospital reviewed and approved the organization’s participation in CRUSADE. Individual informed consent is not required as data were collected anonymously without unique patient identifiers and there were no specific research-related interventions that represented a significant patient risk.

Study Population
The study population for our analysis included 30,136 CRUSADE patients enrolled in 387 hospitals between January 1 and September 30, 2004. Patients with missing weight (n=826) or missing creatinine clearance (n=1120) data were excluded from dosing calculations that required these variables. Patients who had coronary artery bypass grafting (n=2730) or who were transferred out of a participating hospital (n=3784) were excluded from bleeding analyses due to confounding with post-coronary artery bypass graft bleeding, and other outcome analyses were excluded due to incomplete follow-up. Patients were classified into 3 groups according to antithrombotic therapies received: UFH, LMWH, and glycoprotein IIb/IIIa inhibitors.

Definitions
We describe the initial bolus and infusion rates of antithrombotic therapies administered during the first 24 hours to patients with NSTE ACS. Recommended antithrombotic dose was defined in accordance with package inserts, guidelines, and clinical trial publications (TABLE 1). 11,18,31 Based on these recommendations, the following dosing categories were defined: underdosed, recommended, and excess. Excess dosing was further subdivided into mild and major excess. No excess included doses within or below the recommended range. For UFH, total bolus (U) and infusion (U/h) were divided by total body weight (kg) as recorded on the case report form to determine delivered bolus (U/kg) and infusion dose (U/kg per hour). For LMWH, total dose (mg) was divided by total body weight (kg) to determine delivered dose (mg/kg). Interval frequency for LMWH was not collected; therefore, dosing reflects adjustment based on body weight only. Creatinine clearance was estimated from age, sex, creatinine, and body weight as recorded on the case report form by using the formula of Cockcroft-Gault. 27 For glycoprotein IIb/IIIa inhibitors, dose was collected as either full or reduced dose as follows: eptifibatide full dose (2 µg/kg per minute) or reduced dose (1 µg/kg per minute), or tirofiban full dose (0.1 µg/kg per hour) or reduced dose (0.05 µg/kg per hour).

Race was collected as reported in the medical record (white, black, Asian, Pacific Islander, American Indian, or other). Hypertension was determined by a patient having a systolic blood pressure of more than 140 mm Hg, diastolic blood pressure of more than 90 mm Hg on repeated measurements, or hypertension chronically treated with antihypertensive medications. Renal insufficiency was determined by a serum creatinine level of more than 2.0 mg/dL (>176.8 µmol/L), creatinine clearance of less than 30 mL/min (<0.50 mL/s), or need for renal dialysis.

Major bleeding was defined as any intracranial hemorrhage, transfusion of at least 2 units of packed red blood cells, or absolute drop in hematocrit of at least 12%, similar to definitions used in trials and other registries. 29 Death was defined as in-hospital death and length of stay was the number of days between admission and discharge.

Hospital quality performance was determined by overall adherence to 9
quality indicators of American College of Cardiology/American Heart Association guideline-recommended care in NSTE ACS. These indicators included the use of 4 acute therapies (aspirin, β-blockers, heparin, and glycoprotein IIb/IIIa inhibitors) and 5 discharge therapies (aspirin, clopidogrel, β-blockers, angiotensin-converting enzyme inhibitors, and lipid-lowering agents) in patients with indications but no contraindications.29 Hospitals were categorized into quartiles based on high- and low-adherence scores for comparison.

Analysis
Patient characteristics, presentation, treatment, and hospital characteristics are shown for the overall population according to antithrombotic therapy group. Continuous variables are reported as medians and interquartile ranges or mean (SD), and categorical variables are reported as number (percentage). Significance was determined using χ² tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

We investigated patient and physician factors associated with excess dosing for each therapy by using multivariable analysis with the generalized estimating equations method to adjust for associations within clustered responses (eg, within hospital associations).30 The factors in these analyses included age, sex, weight, renal insufficiency, prior congestive heart failure (CHF), diabetes mellitus, academic hospital status, cardiologist as primary physician, and hospital score for adherence to guideline-recommended medications. In addition, the proportion of patients receiving excess dose is demonstrated as a function of age (<65 years, 65-74 years, and ≥75 years).

Our primary goal was to compare outcomes in patients receiving excess doses compared with no excess dose. Secondary analyses also explored the relationship between the magnitude of excess dose and multiple agents dosed in excess. Major bleeding was determined for excess compared with no excess, and for mild and major degrees of excess compared with recommended dose. For patients treated with both glycoprotein IIb/IIIa inhibitors and heparins, major bleeding if neither, either, or both were administered in excess dose was determined. Using general estimating equations, major bleeding was adjusted for key variables known to increase risk of bleeding in an NSTE ACS population (eg, age, renal insufficiency, female sex, signs of CHF on admission, and systolic blood pressure).21 Adjustment was performed for each agent individually and for multiple antithrombotic agents. In addi-

Table 1. Dosing Recommendations and Categories for Antiplatelet and Antithrombin Agents for Non–ST-Segment Elevation Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Dosing Categories</th>
<th>Dosing Recommendations</th>
<th>Recommended</th>
<th>Excess</th>
<th>Mild Excess</th>
<th>Major Excess</th>
<th>Underdosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Bolus of 60-70 U/kg followed by an infusion of 12-15 U/kg per hour.1 Elderly patients (&gt;60 y) may require lower heparin doses.11,12</td>
<td>Bolus 60-70 U/kg and/or infusion 12-15 U/kg per hour</td>
<td>Bolus &gt;70 U/kg or an infusion &gt;15 U/kg per hour</td>
<td>Bolus 70-80 U/kg or infusion 15-20 U/kg per hour</td>
<td>Bolus &gt;80 U/kg or infusion of &gt;20 U/kg per hour</td>
<td>Bolus &lt;60 U/kg and infusion &lt;12 U/kg</td>
</tr>
<tr>
<td>Low-molecular-weight heparin</td>
<td>Enoxaparin: 1 mg/kg subcutaneously every 12 hours.1 Dose reduction by 50% if creatinine clearance &lt;30 mL/min by increasing interval to every 24 hours. Elderly patients at high risk of bleeding.13,14 Dalteparin: use caution in elderly patients with low body weight or predisposed to renal insufficiency15,16</td>
<td>0.95-1.05 mg/kg</td>
<td>&gt;1.05 mg/kg</td>
<td>1.05-1.20 mg/kg</td>
<td>&gt;1.20 mg/kg</td>
<td>&lt;0.95 mg/kg</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>Eptifibatide: bolus 180 µg/kg and infusion of 2.0 µg/kg per minute for 72-96 hours. Reduce infusion rate by 50% to 1 µg/kg per minute if creatinine clearance &lt;50 mL/min or serum creatinine of 2-4 mg/dL.17,18</td>
<td>Full dose unless dose reduction indicated</td>
<td>Tiopronin full dose if creatinine clearance &lt;30 mL/min or epifibatide full dose if creatinine clearance &lt;50 mL/min</td>
<td>Excess dosing in those patients with serum creatinine ≤2.0 mg/dL</td>
<td>Excess dosing in those patients with serum creatinine &gt;2.0 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

SI conversions: To convert creatinine clearance to mL/s, multiply by 0.0167; serum creatinine to µmol/L, multiply by 88.4.
*Dosing recommendations from guidelines and product labels. Mild and major excess categories are subgroups of excess dosing category.
†Insufficient numbers for underdosing of glycoprotein IIb/IIIa inhibitors group.
tion, the relationship between excess dosing and in-hospital death and length of stay was adjusted for age, sex, race, body mass index (calculated as weight in kilograms divided by the square of height in meters), renal insufficiency, cardiac risk factors, prior cardiac history, electrocardiogram changes, positive cardiac markers, signs of CHF, systolic blood pressure, and heart rate at admission. A 2-sided \( P < .05 \) was considered statistically significant. All analyses were performed by using SAS software version 8.2 (SAS Institute, Cary, NC).

**RESULTS**

We determined antithrombotic dosing for patients with NSTE ACS in hospitals across the United States, in which 8447 (28%) received care at an academic hospital, 22516 (75%) at a hospital with on-site cardiac surgical services, and 17156 (57%) were treated primarily by cardiologists. A total of 24315 patients with NSTE ACS (87.2%) received heparin and 13967 (56.1%) received a glycoprotein IIb/IIIa inhibitor. There were minor differences between those patients receiving UFH and LMWH, with patients receiving LMWH tending to be older, more often women, and more likely to have a history of CHF (TABLE 2). In addition, patients treated with LMWH were less likely to be administered a glycoprotein IIb/IIIa inhibitor or undergo a cardiac catheterization or percutaneous coronary intervention compared with patients initially administered UFH. Use of LMWH was also more common in smaller nonacademic hospitals.

Patients receiving glycoprotein IIb/IIIa inhibitors were younger, more often men, weighed more and had better renal function than those who received any heparin. Patients receiving glycoprotein IIb/IIIa inhibitors within the first 24 hours were also more likely to have positive cardiac markers, more often had catheterization and percutaneous coronary intervention, but less often had coronary artery bypass grafting during their hospital stay.

**Table 2. Patient and Treatment Variables by Initial Antithrombotic Therapy**

<table>
<thead>
<tr>
<th>Population</th>
<th>Overall (N = 30,136)</th>
<th>Unfractionated Heparin (n = 13,298)</th>
<th>Low-Molecular-Weight Heparin (n = 12,526)</th>
<th>Glycoprotein IIb/IIIa Inhibitors (n = 13,967)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y†</td>
<td>68 (56-79)</td>
<td>65 (55-76)</td>
<td>68 (57-78)</td>
<td>63 (54-73)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>42.6 (12,822)</td>
<td>47.8 (4632)</td>
<td>42.8 (5355)</td>
<td>53.9 (7590)</td>
</tr>
<tr>
<td>65-74</td>
<td>22.5 (6773)</td>
<td>22.8 (3030)</td>
<td>22.8 (2859)</td>
<td>23.4 (3267)</td>
</tr>
<tr>
<td>≥75</td>
<td>34.8 (10,480)</td>
<td>39.2 (3885)</td>
<td>34.2 (4287)</td>
<td>22.5 (3147)</td>
</tr>
<tr>
<td>Women</td>
<td>39.4 (11,823)</td>
<td>35.8 (4760)</td>
<td>39.5 (4951)</td>
<td>32.8 (4578)</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>18.3 (5501)</td>
<td>19.2 (2546)</td>
<td>16.7 (2094)</td>
<td>16.7 (2329)</td>
</tr>
<tr>
<td>BMI†</td>
<td>28 (25-32)</td>
<td>28 (25-32)</td>
<td>28 (25-32)</td>
<td>28 (25-32)</td>
</tr>
<tr>
<td>Weight, kg†</td>
<td>81 (68-95)</td>
<td>82 (70-96)</td>
<td>81 (69-93)</td>
<td>84 (72-98)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>27.2 (8200)</td>
<td>30.7 (4080)</td>
<td>27.9 (3496)</td>
<td>34.2 (4777)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33.1 (9967)</td>
<td>31.6 (4223)</td>
<td>32.8 (4160)</td>
<td>29.3 (4096)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68.9 (21,060)</td>
<td>69.0 (6177)</td>
<td>70.0 (8772)</td>
<td>65.9 (9210)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>13.2 (3889)</td>
<td>12.5 (1662)</td>
<td>10.7 (1338)</td>
<td>6.8 (944)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min†</td>
<td>54 (35-75)</td>
<td>58 (38-79)</td>
<td>55 (37-76)</td>
<td>64 (46-84)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>83 (70-98)</td>
<td>82 (70-96)</td>
<td>83 (70-98)</td>
<td>80 (68-93)</td>
</tr>
<tr>
<td>Positive cardiac markers</td>
<td>87.6 (26,400)</td>
<td>88.7 (11,789)</td>
<td>89.1 (11,162)</td>
<td>89.9 (12,555)</td>
</tr>
<tr>
<td>Signs at presentation‡</td>
<td>34.4 (10,352)</td>
<td>35.8 (4765)</td>
<td>32.8 (4111)</td>
<td>34.5 (4820)</td>
</tr>
<tr>
<td>Signs of CHF‡</td>
<td>23.4 (7065)</td>
<td>20.4 (2708)</td>
<td>23.0 (2880)</td>
<td>15.0 (2000)</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg‡</td>
<td>144 (124-166)</td>
<td>145 (124-166)</td>
<td>146 (127-167)</td>
<td>146 (127-166)</td>
</tr>
<tr>
<td>ST-segment depression‡</td>
<td>3.5 (1.8-2.4)</td>
<td>3.6 (1.8-2.5)</td>
<td>3.6 (1.8-2.5)</td>
<td>3.6 (1.8-2.5)</td>
</tr>
<tr>
<td>Treatment variables§</td>
<td>47.7 (13,298)</td>
<td>100 (13,298)</td>
<td>12.1 (1,509)</td>
<td>55.2 (7584)</td>
</tr>
<tr>
<td>Acute unfractionated heparin</td>
<td>44.9 (12,526)</td>
<td>11.4 (1509)</td>
<td>100 (12,526)</td>
<td>45.2 (6218)</td>
</tr>
<tr>
<td>Acute low-molecular-weight heparin</td>
<td>56.1 (13,967)</td>
<td>65.2 (7584)</td>
<td>57.5 (6218)</td>
<td>100 (13,967)</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>78.8 (19,806)</td>
<td>86.7 (10,117)</td>
<td>79.0 (8,425)</td>
<td>90.7 (12,020)</td>
</tr>
<tr>
<td>Cardiac catheterization</td>
<td>49.6 (10,914)</td>
<td>58.4 (6131)</td>
<td>47.8 (4293)</td>
<td>74.3 (8785)</td>
</tr>
<tr>
<td>PCI§</td>
<td>12.3 (26,499)</td>
<td>13.5 (1415)</td>
<td>13.4 (1202)</td>
<td>9.7 (1114)</td>
</tr>
<tr>
<td>CABG§</td>
<td>28.0 (8447)</td>
<td>36.0 (4790)</td>
<td>21.6 (2707)</td>
<td>29.9 (4173)</td>
</tr>
<tr>
<td>No. of beds†</td>
<td>365 (236-501)</td>
<td>376 (245-536)</td>
<td>351 (234-487)</td>
<td>377 (248-526)</td>
</tr>
<tr>
<td>Cardiologist as primary physician</td>
<td>56.9 (17,156)</td>
<td>64.1 (8527)</td>
<td>56.4 (7060)</td>
<td>69.1 (9653)</td>
</tr>
<tr>
<td>Cardiac surgery available</td>
<td>74.7 (22,516)</td>
<td>80.1 (10,654)</td>
<td>72.6 (9091)</td>
<td>80.3 (11,218)</td>
</tr>
<tr>
<td>US geographic region</td>
<td>32.0 (9651)</td>
<td>24.5 (3252)</td>
<td>40.5 (3371)</td>
<td>32.6 (4548)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass grafting; CHF, congestive heart failure; PCI, percutaneous coronary intervention.

\( P \) = Probability. Denominators vary slightly by variable from column totals due to missing values and removing those patients with known contraindications from the denominator. Glycoprotein IIb/IIIa inhibitors include either eptifibatide or tirofiban. See “Methods” for definitions of patient characteristics.

*Presented as median (interquartile range).

†Signs of CHF are indicated by exertional dyspnea, orthopnea, shortness of breath, labored breathing, fatigue at either rest or with exertion, rates of more than one third of the lung fields, increased jugular venous pressure, S3 gallop, or pulmonary congestion on radiograph believed to represent cardiac dysfunction.

§Presented only among those without contraindications for each agent.

*Academic affiliation reflects listing in Council of Teaching Hospitals; others were nonacademic. Cardiac procedural services available at participating hospitals ranged from none, cardiac catheterization only, coronary intervention only, or full services including cardiac surgery. The attending physician serving as primary physician for the patient during the hospitalization was ascertained by the most frequent and consistent notations in the medical record; specialties included cardiologist, internist, family practitioner, and other.

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compared with the overall population. A cardiologist was also more likely to be involved in the care of patients who received glycoprotein IIb/IIIa inhibitors and UFH.

**Antithrombotic Dosing**

Recommended UFH dose was administered 30.3% of the time, recommended LMWH dose was administered 53.8% of the time, and recommended glycoprotein IIb/IIIa inhibitor dose was administered 72.3% of the time. Forty-two percent of the population (n=3354) treated with at least 1 antithrombotic agent received it in an excess dose. UFH was administered in excess to 32.8% of those patients who received it (n=2934). Of those patients administered excess UFH, 922 (31.5%) received only bolus in excess (>70 mg/kg), 616 (21.0%) received only infusion in excess (>15 mg/kg), and 1392 (47.5%) received excess of both. Excess dosing of LMWH and glycoprotein IIb/IIIa inhibitors occurred in 1378 patients (13.8%) and 2784 patients (26.8%), respectively. Among 7983 patients administered both heparin (UFH or LMWH) and a glycoprotein IIb/IIIa inhibitor, 2799 (35%) received an excess of one or the other and 555 (7%) received excess of both.

The majority of excess dosing was mild in degree, but a small proportion of patients were administered doses far above the recommended range (major excess). For UFH, 2639 patients (29.5%) received mild excess and 882 (9.9%) received major excess. For LMWH, 1261 patients (12.6%) received mild excess and 310 (3.1%) received major excess. For the 10 379 patients who received glycoprotein IIb/IIIa inhibitor, 2565 (24.7%) received mild excess and 219 (2.1%) received major excess. The majority of patients (92.1% [2565/2784]) who received excess glycoprotein IIb/IIIa inhibitors as determined by renal function had a serum creatinine level of 2 mg/dL or less (≤176.8 µmol/L).

A number of patients also received initial antithrombotic therapy at doses lower than recommended. Underdosing occurred in 2710 patients (30.3%) who received UFH and 3041 patients (30.5%) who received LMWH. Only 93 (1.2%) of 7595 patients with normal renal function received renally adjusted doses of glycoprotein IIb/IIIa inhibitors.

**Predictors of Excess Dose**

The effect of patient age on the likelihood of receiving excess doses is shown in FIGURE 1. Elderly patients aged 75 years or older were more likely to receive excess doses of antithrombotic agents compared with patients younger than 65 years (16.5% [n=561] vs 12.5% [n=536] for LMWH, 38.4% [n=994] vs 28.7% [n=1235] for UFH, and 64.5% [n=1495] vs 8.5% [n=477] for glycoprotein IIb/IIIa inhibitors). TABLE 3 shows the adjusted predictors of excess dosing. In addition to age, renal in-

**Table 3. Patient-Level and Practice-Level Predictors of Excess Antithrombotic Dose**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unfractionated Heparin</th>
<th>Low-Molecular-Weight Heparin</th>
<th>Glycoprotein IIb/IIIa Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0.93 (0.79-1.11)</td>
<td>0.76 (0.65-0.89)</td>
<td>4.23 (3.67-4.86)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.81 (0.68-0.96)</td>
<td>0.75 (0.63-0.89)</td>
<td>14.39 (12.24-16.90)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>1.25 (1.07-1.46)</td>
<td>0.82 (0.67-1.00)</td>
<td>4.12 (2.96-5.75)</td>
</tr>
<tr>
<td>Women</td>
<td>0.92 (0.80-1.00)</td>
<td>0.73 (0.63-0.84)</td>
<td>3.74 (2.90-4.25)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.04 (0.93-1.16)</td>
<td>1.16 (1.03-1.31)</td>
<td>1.35 (1.20-1.51)</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>0.86 (0.73-1.02)</td>
<td>1.14 (0.97-1.33)</td>
<td>1.49 (1.23-1.81)</td>
</tr>
<tr>
<td>Weight, per 5-kg decrease</td>
<td>1.28 (1.22-1.35)</td>
<td>1.26 (1.23-1.29)</td>
<td>1.02 (1.00-1.04)</td>
</tr>
<tr>
<td>Academic hospital</td>
<td>1.02 (0.66-1.58)</td>
<td>1.26 (1.03-1.54)</td>
<td>0.93 (0.76-1.15)</td>
</tr>
<tr>
<td>Cardiologist</td>
<td>0.90 (0.77-1.06)</td>
<td>1.17 (1.02-1.34)</td>
<td>0.94 (0.82-1.06)</td>
</tr>
<tr>
<td>Medication adherence, per 5% decrease</td>
<td>1.12 (0.97-1.30)</td>
<td>1.02 (0.97-1.08)</td>
<td>1.06 (1.01-1.12)</td>
</tr>
</tbody>
</table>

**Figure 1. Excess Dose as a Function of Patient Age**

The percentage of patients receiving excess of each agent among all patients receiving each agent are shown by 3 age groups (<65 years, 65-74 years, and ≥75 years); P<.001 for all 3 treatment groups. Standard errors are all less than 1.5%. Numbers provided are the individuals receiving treatment with available dose information in each age group.
sufficiency, female sex, diabetes mellitus, prior CHF, and weight impacted a patient’s likelihood for receiving an excess dose. We explored the relationship between excess dosing and physician and process variables. Patients treated at hospitals without academic affiliation were more likely to receive excess UFH (35.9% [n=2019] vs 27.5% [n=911], P<.001) and glycoprotein IIb/IIIa inhibitors (27.5% [n=2024] vs 25.3% [n=760], P=.03). This association and other physician variables did not remain significant after adjustment (Table 3). However, patients treated at hospitals with worst adherence to guideline-recommended treatment were more likely to receive excess UFH (39.0% [n=532] vs 28.1% [n=697], P<.001), LMWH (15.0% [n=284] vs 12.4% [n=325], P=0.8), and glycoprotein IIb/IIIa inhibitors (31.2% [n=921] vs 24.9% [n=867], P<.001) than those treated at hospitals with best adherence. After adjustment, hospitals with lower adherence to guidelines continued toward giving excess heparin doses and were significantly more likely to give excess glycoprotein IIb/IIIa inhibitors.

**Major Bleeding**

Major bleeding occurred in 11.5% (2726/23 622) of the noncoronary artery bypass grafting and nontransfer CRUSADE population. Increases in major bleeding occurred in 127 patients (12.5%) with excess LMWH, 319 (13.6%) with excess UFH, and 374 (17.5%) with excess glycoprotein IIb/IIIa inhibitors. After adjustment, those patients receiving excess doses of UFH demonstrated a slight trend to increased bleeding (odds ratio [OR], 1.08; 95% confidence interval [CI], 0.94–1.26); although those patients receiving excess LMWH (OR, 1.39; 95% CI, 1.11–1.74) or glycoprotein IIb/IIIa inhibitors (OR, 1.36; 95% CI, 1.10–1.68) had significantly more bleeding compared with patients not administered excess doses.

There was also a dose-response relationship between the magnitude of excess dose and bleeding for all 3 agents (Figure 2). After adjustment, patients receiving mild excess of UFH had similar rates of bleeding to those receiving recommended doses (OR, 1.01; 95% CI, 0.83–1.23), while those receiving major excess had significant increased bleeding (OR, 1.31; 95% CI, 1.02–1.68). After adjustment, patients receiving mild excess of LMWH had similar rates of bleeding to those receiving recommended doses (OR, 1.28; 95% CI, 0.97–1.68), while those receiving major excess had significant increased bleeding (OR, 1.66; 95% CI, 1.14–2.40). Finally, after adjustment, any degree of excess glycoprotein IIb/IIIa inhibitor significantly increased bleeding risk (mild: OR, 1.26; 95% CI, 1.03–1.55; and major: OR, 2.55; 95% CI, 1.53–4.25) compared with recommended doses. Among those patients administered both heparin and glycoprotein IIb/IIIa agents, bleeding increased as a function of the number of agents excessively dosed and was highest when both heparin and glycoprotein IIb/IIIa inhibitors were administered in excess (neither, 6.6% [n=237]; either, 13.4% [n=287]; or both, 22.2% [n=93]). After adjustment, when both were administered in excess, the risk for major bleeding increased 2-fold (OR, 1.97; 95% CI, 1.48–2.64).

Underdosing of UFH did not significantly alter bleeding risk (adjusted OR, 1.14; 95% CI, 0.93–1.39), although patients underdosed with LMWH tended to bleed more (adjusted OR, 1.19; 95% CI, 1.00–1.42).

**Mortality and Length of Stay**

Patients receiving excess antithrombotic therapy also had higher mortality and longer length of stays. Compared with recommended doses, mild and major excesses of UFH (3.8% [n=78] vs 3.9% [n=80] and 5.8% [n=41], respectively; P=.04), LMWH (2.5% [n=101] vs 3.3% [n=30] and 3.4% [n=8], respectively; P=.08), and glycoprotein IIb/IIIa inhibitors (1.2% [n=73] vs 4.3% [n=83] and 12.4% [n=22], respectively; P<.001) were all associated with higher mortality. However, higher mortality persisted after adjustment only for excess glycoprotein IIb/IIIa inhibitors (adjusted OR, 1.50; 95% CI, 1.03–2.17). Length of stay was longer in those patients administered excess doses for UFH (mean [SD], 4.6 [3.7] to 4.9 [4.1] days; P=.006), LMWH (4.7 [4.2] to 5.1 [4.0] days, P=.002),

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and glycoprotein IIb/IIIa inhibitors (3.8 [3.0] to 5.2 [4.0] days, \( P < .001 \)) compared with patients not receiving excess doses.

**Attributable Risk**

Although it is not possible to firmly establish a causal link between excess dosing and major bleeding in an observational study, we estimated the potential impact of dose-associated bleeding in our population as follows. The relative increase in bleeding with excess dosing (rate of bleeding in patients receiving excess dose minus rate of bleeding in those not dosed excessively) was applied to the total number of patients receiving excess doses of each agent to arrive at the incremental dose-associated bleeding. Results by therapy were a 2.2% relative increase in bleeding (53 events) for 2390 patients who received excess UFH, a 4.0% relative increase in bleeding (55 events) for 1378 patients who received excess LMWH, and a 10.5% relative increase in bleeding (292 events) for 2784 patients who received excess glycoprotein IIb/IIIa inhibitors. By dividing dose-associated bleeding by all bleeding events, we determined that as much as 15% (400/2766) of major bleeding events in CRUSADE may be attributable to excess dosing.

**COMMENT**

As far back as the 15th century, the importance of the therapeutic window was acknowledged by Paracelsus, the father of modern pharmacology, who stated, “All drugs are poisons, the benefit depends on the dosage.” Although prior studies have focused on errors of omission (failure to give effective medicines to eligible patients), our study demonstrates errors of commission (failure to give those medicines correctly). In the CRUSADE registry, more than 42% of all patients with NSTE ACS who receive recommended doses of thinner one. By ensuring creatinine clearance and weight are available at admission, some aspects of dosing accuracy may be improved. Additionally, dosing guides on standard order forms, clinical pharmacists on rounds, and multidisciplinary teams can double-check dosing accuracy. Studies have also found that computerized order entry systems can help with the identification of dosing errors. Interestingly, we found an association between errors of omission (failure to give recommended therapies) and errors of commission (dosing errors) at the hospital level. Specifically, centers with higher use of guideline-recommended therapies have lower rates of dosing errors. This may reflect physician experience or the safety environment at these locations (ie, evidence-based medicine practice tools, quality improvement processes, or staff protocols).

**Association of Dosing With Outcomes**

Our study further links excess dosing with an increased risk of bleeding even after adjustment for numerous potential confounders. Bleeding is financially costly and associated with worse patient outcomes with 3-fold higher mortality demonstrated in a similar NSTE ACS population (major bleeding, 18.6% vs no bleeding, 5.1%).

We demonstrate that patients who receive excess antithrombotic therapy have higher mortality and longer lengths of stay presumably due to bleeding events. Bleeding also demonstrates a dose-response with greatest risk among those patients receiving the most excess (major excess) or multiple agents in excess dose. On the other hand, our data demonstrate the potential safety of antithrombotic therapy when dosed appropriately. Specifically, patients with NSTE ACS who receive recommended doses of heparin and glycoprotein IIb/IIIa inhibitors alone or in combination have the lowest rates of bleeding. This suggests that safety profiles observed in clinical trials may be attainable in community populations with improved dosing.
ing accuracy. The interesting increase in bleeding risk with underdosing of LMWH may reflect unmeasured confounders or intentional underdosing of those patients known to be highest risk in the clinical setting. In addition, the risk gradient observed with major excesses should not diminish the importance of mild excess, as we show that any excess dosing is potentially adverse.

**Study Limitations**

CRUSADE hospitals voluntarily participate in this national quality improvement initiative; therefore, their focus on quality may actually underestimate the magnitude of excessive dosing in general community practice. Consecutive patient enrollment in CRUSADE was requested but cannot be monitored. Similarly, completeness and accuracy of the CRUSADE database was high in an audited sample, but events are not adjudicated and underreporting is possible. These factors, if anything, would lead to an underestimation of dosing errors as well as their association with adverse clinical outcomes. Subsequent dosing adjustments made after the initial dose were delivered or alterations in dosing interval for LMWH were not considered. The cut points for mild and major excess were selected for demonstration purposes only, and dosing risk is likely to increase along a continuum. In addition, due to a lack of accurate information on recurrent ischemic events and/or reinfection in CRUSADE, we could not investigate the potential harm resulting from underdosing effective therapies in our study.

**Conclusions**

Although the value of antithrombotic therapy for NSTE ACS is well established, dosing errors are common in community practice and are associated with an increased risk of major bleeding. The expanding array of therapies coupled with the aging population makes attention to dosing an immediate priority for safe NSTE ACS care. With more than 1 million patients admitted to US hospitals each year with NSTE ACS, preventing bleeding events in this population would yield substantial health and cost benefits.

**Author Contributions:** Dr Alexander had full access to all of 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:** Alexander, Roe, Gliber, Ohman, Peterson.

**Acquisition of data:** Alexander, Roe, Pollack, Ohman, Peterson.

**Analysis and interpretation of data:** Alexander, Chen, Roe, Newby, Gibson, Allen-LaPointe, Pollack, Ohman, Peterson.

**Drafting of the manuscript:** Alexander, Peterson.

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**Statistical analysis:** Alexander, Chen.

**Obtained funding:** Roe, Pollack, Gliber, Ohman, Peterson.

**Administrative, technical, or material support:** Alexander, Roe, Allen-LaPointe, Pollack, Gliber, Peterson.

**Study supervision:** Alexander, Roe, Gibson, Peterson.

**Financial Disclosures:** Additional Information: None of the sponsors played a role in conducting the study or in interpreting or reporting the results. None of the authors other than Dr Alexander had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data. These factors, if anything, would lead to an underestimation of dosing errors as well as their association with adverse clinical outcomes. Subsequent dosing adjustments made after the initial dose were delivered or alterations in dosing interval for LMWH were not considered. The cut points for mild and major excess were selected for demonstration purposes only, and dosing risk is likely to increase along a continuum. In addition, due to a lack of accurate information on recurrent ischemic events and/or reinfection in CRUSADE, we could not investigate the potential harm resulting from underdosing effective therapies in our study.

**REFERENCES**


Limitations of our study include that, as a cohort study, there is a potential that unmeasured confounders caused the observed differences. Small sample size and few outcomes in some of the subgroups also limit the ability to reach definitive conclusions and may account for some of the differences in results compared with Berk et al.1 As a post hoc analysis, the findings should be considered hypothesis generating. Given these factors, there is a need for randomized trials of treatment for perinatal HIV infection to understand the optimal methods of preventing disease progression. Consideration must also be given to treatment in countries where triple therapy is not available.

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Financial Disclosures: None reported.

CORRECTIONS

Incorrect Units: In the Original Contribution entitled “Excess Dosing of Antiplatelet and Antithrombin Agents in the Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes” published in the December 28, 2005, issue of JAMA (2005; 294:3108-3116), although correct in the dosing recommendation table (Table 1), incorrect units for tirofiban were printed in the accompanying text. On page 3109, the units for tirofiban should have been µg/kg per minute, not µg/kg per hour.