Dose Capping Enoxaparin Is Unjustified and Denies Patients With Acute Coronary Syndromes a Potentially Effective Treatment

To the Editor:

We read with interest the article from Macie et al (May 2004)1 highlighting the importance of adhering to the correct dosing of enoxaparin for the prevention of ischemic events in patients with unstable angina or non–ST-segment elevation myocardial infarction. The article adds to the current controversy over dosing practices for enoxaparin in obese patients, while discussing the risk factors for increased bleeding. We would like to add the following points:

The optimal dose of enoxaparin for treatment of acute coronary syndromes (ACS) is 1 mg/kg, and this dose should be adhered to—ie, no more and no less.2 There is evidence that when the dose is adjusted down unnecessarily, survival and efficacy is reduced, thus emphasizing the importance of a correct dosing regimen.3 There is evidence that the 100-mg capped dose used in this study is unnecessary, both in terms of the pharmacokinetics of enoxaparin in obese volunteers and its safety and efficacy in ACS patients.4,5,6 In fact, there is no evidence to suggest the need to modify the currently recommended dose of enoxaparin for treatment of venous thromboembolism and ACS in obese patients.7 The 100-mg capped dose applicable in Canada goes against all known data, arising from a demand from the Canadian Health Authority that is supported by neither clinical trial data nor the recommendation of the manufacturer. We can only speculate as to the rationale behind this labeling requirement. When the effect of low-molecular-weight heparin (LMWH) in protecting against new cardiac events in unstable coronary artery disease (CAD) was looked at, the Fragmin During Instability in Coronary Artery Disease study8 capped the dosage of dalteparin at 10,000 IU and dalteparin was the first LMWH licensed in Canada for ACS. However, because different LMWHs have different pharmacologic profiles and recommended doses, the results obtained with one LMWH preparation should not be extrapolated to another.9 It is interesting to note that the subsequent Fragmin in Unstable Coronary Artery Disease Study trial had no mention of a capped dose and used a patient-weight range > 150 kg.9

It was stated in the article by Macie et al10 that previous randomized controlled trials (RCTs) have limitations in addressing practical issues that may impact on bleeding risk in the real-world population, because of the exclusion of patients weighing > 100 kg. First, the prespecified definition of obesity should use body mass index (BMI), because body weight alone is not always an accurate reflection of obesity. For example, the heaviest weight recorded in the Thrombolysis in Myocardial Infarction (TIMI) 11B11 and Efficacy and Safety of Subcutaneous Enoxaparin in NonQ-Wave Coronary Events (ESSENCE)12 databases for a nonobese patient is 110 kg. Second, it is untrue that other studies have not researched patients weighing > 100 kg; in the meta-analysis of the TIMI 11B and ESSENCE trials comparing the safety and efficacy of a weight-adjusted dose of enoxaparin and unfractionated heparin (UFH) in obese patients (n = 7,081), approximately 26% of patients in the trial were obese (defined as BMI ≥ 30), thereby providing a large sample size for comparison.8 The maximum weight of patients treated with enoxaparin in this meta-analysis was 158.6 kg. Of these patients, 540 patients weighed > 100 kg (n = 275 UFH, n = 265 enoxaparin). Statistical analysis on this subgroup showed no significant difference between the UFH and enoxaparin groups in either the double or triple end points (incidence of death and myocardial infarction and/or urgent revascularization). Meanwhile, the maximum weight of patients in the Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial,12 which evaluated the effect of enoxaparin and UFH on death and myocardial infarction in high-risk patients presenting with non–ST-segment elevation ACS (n = 10,027), was 175 kg in the UFH group and 196 kg in the enoxaparin group, while the interquartile range was 70 to 91 kg for both groups—the highest weights for any ACS trial to date. There were no inclusion/exclusion criteria related to weight, and dosing was 1 mg/kg for all patients. Recent preliminary results from the SYNERGY trial have shown no evidence of differing efficacy or safety between 1 mg/kg weight-adjusted enoxaparin and UFH in the obese subgroup (K.W. Mahaffey, MD; personal communication; September 24, 2004). To our knowledge, there has only been one clinical trial13 of enoxaparin in patients with ACS where there was a weight cutoff at 110 kg. Third, the studies referenced for this statement are a pharmacodynamic study of tinzaparin and a pharmacokinetic study on the effect of weight and LMWH in the treatment of venous thromboembolism (ie, no ACS patients).

In the study by Macie et al,1 the authors report that increased length of treatment was related to bleeding: one should question whether incorrect dosing also impacted on bleeding and whether this was tested in the bleeding risk model. For instance, what was the incidence of major bleeding in the 17 patients who received a dose > 3 mg/kg? It is also important to note that the major bleeding definition used by Macie et al1 was less stringent than that used in TIMI 11B and ESSENCE—with the definition in the study by Macie et al including a hemoglobin drop of 20 g/L in place of 30 g/L. It is therefore difficult to compare bleeding rates, because one could expect rates to be higher in the study by Macie et al1 compared with the RCTs.

When “any bleeding episode” is recorded as a safety end point, subcutaneous administration in obese patients is expected to cause a higher incidence of ecchymosis and hematoma (at the injection site) compared with IV administration. In a real-world setting—an analysis of 13,231 ACS patients in the Global Registry of Acute Coronary Events (GRACE)—major bleeding rates have been reported to be 2.1% in patients receiving a LMWH (of which 80.1% received enoxaparin) vs 4.9% in those receiving UFH.14

With regard to the reported risk factors that increase bleeding risk with enoxaparin, advance age and renal insufficiency have also been reported in GRACE19 to be independent predictors of bleeding, ie, independent of LMWH use. Dose adjustment of the standard of 1 mg/kg qd dose of enoxaparin is recommended by the manufacturer in patients with severe renal impairment (creatinine clearance < 30 mL/min), because enoxaparin is renally cleared (according to the prescribing information of the
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tation and coronary artery bypass surgery, were not evaluated in the study by Macie et al.3 Since > 50% of patients go on to undergo a coronary procedure, it questions the real-world validity of this investigation. Patients in SYNERGY who received consistent enoxaparin therapy (patients who started on a certain therapy and stayed on that original therapy throughout the trial) and under-

went early percutaneous coronary intervention had numerically less major bleeding than patients receiving UFH (1.3% of patients had Global Utilization of Streptokinase and Tissue Plasminogen Activator to Open Occluded Coronary Arteries trial bleeding compared with 1.7% using UFH).16 There is also a disconnect between patient care observed in this study and our practice experience: low-risk patients with ACS who do not require transfer for revascularization are not hospi-

talized for 10 days in our practice (as was average in the study). It appears from the results of the study by Macie et al1 that enoxaparin treatment at 1 mg/kg was not evaluated for safety (ie, increased bleeding risk with increased dose). In addition, the authors did not evaluate whether or not patients who received > 100 mg per dose had higher rates of bleeding. Therefore, we cannot concur with the authors’ recommendations that the dose of enoxaparin should be capped at 100 mg. We see no evidence to suggest the validity of a dose-capping regimen for enoxaparin in obese patients at risk of major bleeding. patients who could potentially be denied an effective treatment therapy.

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9 Klein W, Buchwald A, Hillis SE, et al. Comparison of low-molecular-weight heparin with unfractionated heparin in patients with renal impairment, there were probably more patients with severe impairment than the number noted (3%), because impairment was defined as < 25 mL/min creatinine clearance as opposed to the < 30 mL/min level widely recog-

nized and used as an appropriate cutoff point. Important predictors of bleeding, such as cardiac catheterization and coronary artery bypass surgery, were not evaluated in the study by Macie et al.3 Since > 50% of patients go on to undergo a coronary procedure, it questions the real-world validity of this investigation. Patients in SYNERGY who received consistent enoxaparin therapy (patients who started on a certain therapy and stayed on that original therapy throughout the trial) and under-

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To the Editor:

We thank Drs. Spinler and Dobesh for their letter, and agree that the management of patients with an acute coronary syn-

drome (ACS) who weigh > 100 kg and receive enoxaparin, 1 mg/kg bid, is clinically relevant, as approximately 16% of adults in North America are obese (body mass index > 30 kg/m2), many of whom weigh > 100 kg.1,2 Such patients were underrepresented in the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997; 337:447–452
16 Cohen M, Mahaffey KW, White HD, et al. Enoxaparin 0.3 mg/kg intravenous supplement for patients transitioning to percutaneous coronary intervention: Results from SYN-

observed in our study was unnecessary. In retrospect, we agree. However, this was the practice at our institution during the period of study (from 2000 to 2001), and was consistent with the manufacturer’s guidelines at that time for the use of enoxaparin in patients with an ACS.6

Drs. Spinler and Dobesh question whether incorrect enoxaparin dosing had an effect on bleeding. Despite one in five patients in our study receiving an enoxaparin dose that was > 10% or < 10% of the recommended 1 mg/kg dose, major bleeding did not occur in any of the 17 patients who received a dose > 1 mg/kg. Consequently, enoxaparin dose was not included as a variable in the logistic regression model that assessed determinants of bleeding. The authors also state that our criteria for major bleeding were more liberal than those used in the ESSENCE and TIMI 11B trials, which may have accounted for the higher rate of bleeding in our study (4%) than that observed in the clinical trials (1 to 2%). All patients who had major bleeding had a decrease in hemoglobin > 30 g/L, which would qualify as a major bleed, irrespective of the criteria used. Indeed, there are no accepted standard criteria for major bleeding.7 Furthermore, we never stated the intent to formally compare rates of bleeding across studies.

Drs. Spinler and Dobesh question the lack of a comparator anticoagulant strategy. The prespecified objectives of our study were to assess dosing practices in patients with an ACS who received enoxaparin, not to compare treatment practices with different anticoagulants. The authors also question our use of a creatinine clearance cut-off of < 25 mL/min in our description of the study population. However, this cut-off was used only to describe patients, whereas in the regression analyses, creatinine clearance was a continuous variable when assessed as a predictor of bleeding. Furthermore, the creatinine clearance cut-off of < 30 mL/min, which the authors claim is widely recognized to adjust low-molecular-weight heparin (LMWH) dosing, has never been validated as the cut-point at which LMWH dosing should be adjusted because of concerns of excessive anticoagulation due to impaired renal clearance of LMWH.8

Drs. Spinler and Dobesh question why cardiac catheterization or bypass surgery were not included as predictors of bleeding. As stated in our article, our institution does not support cardiac catheterization; therefore, these procedures could not have been assessed as predictors of bleeding. The authors also state there is a “disconnect” between patient care in our study and that from their experience, questioning why our patients who did not require revascularization were hospitalized, on average, for 10 days. The intent of our study was not to evaluate reasons for length of hospital stay, which we presume would have been related to comorbid conditions, social issues, or lengthy waiting times for cardiac catheterization.

Although Drs. Spinler and Dobesh state that we did not assess the safety of weight-based dosing of enoxaparin (1 mg/kg bid), this was not a prespecified study objective. Furthermore, we did not evaluate bleeding in patients weighing > 100 kg for reasons stated previously. Finally, contrary to the statement of Drs. Spinler and Dobesh, we did not provide any “recommendations” regarding enoxaparin dose capping in patients weighing > 100 kg. What we can all agree on is that using enoxaparin and other LMWHs with a weight-based dosing, irrespective of patient weight, appears effective and safe.9,10

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Assessment of Ventilation During the Performance of Elective Endoscopic-Guided Percutaneous Tracheostomy

To the Editor:

We read with great interest the article by Ferraro et al (July 2004)1 assessing ventilation during elective endoscopic-guided percutaneous tracheostomy, and we have some questions and comments. We agree that bronchoscopic guidance has increased the safety of the procedure and may prevent complications.2,3 We do not agree, however, that the presence of the bronchoscope inside the lumen of the endotracheal tube and trachea produce clinically important airway obstruction leading to hypoventilation, hypercarbia, and hypoxemia.

First, the period during which the bronchoscope is present (ie, from the moment of puncture until dilatation), is relatively short, especially when the Ciaglia Blue Rhino technique is used (Cook; Som, the Netherlands). Indeed, Ferraro et al1 show that the duration of this procedure (from incision of the skin to insertion of the tracheostomy tube) is only 2.45 ± 1.36 min (mean ± SD). Keeping in mind that 1 min of this time period is used for the

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