

Response

To the Editor:

We appreciate the interest demonstrated by Dr Girard and his colleagues in our work.¹ We agree that we cannot completely rule out a selection bias as a mechanism of our findings and have acknowledged this in the “Limitations” section of our article. Despite robustly adjusting for severity of illness in our multivariable regression model, we cannot exclude residual confounding. The “Monday Effect,” or deferred care for relatively minor pulmonary embolism (PE), as suggested by Dr Girard and colleagues, is an interesting concept and deserves further study. Unfortunately, our data sources do not allow us to make such a determination. The National Inpatient Sample has a variable that indicates whether the admission was on a weekday or weekend but not for specific days of the week. However, it is unlikely that this phenomenon is solely responsible for our findings. Delaying care for a potential life-threatening disease, by up to > 2 days in some cases, would lead to an increase in severity of illness and by extension mortality on weekdays in at least some such people. This would bias our results toward finding no differences in mortality between weekends and weekdays.

In our article, we did not mean to suggest that delays in inferior vena cava filter placement might be the direct cause of observed differences in mortality; indeed, we agree with Dr Girard and colleagues that they are unlikely to be a reliable marker of quality of care in acute PE. Rather, we suggest that differences in timeliness of placement may be a surrogate for delays in other processes of care that possibly affect mortality, for example, delays in achievement of anticoagulation targets or impediments in diagnosis via belated performance of CT scan angiography. The proportion of people receiving inferior vena cava filters in our study is consistent with other investigations in the United States.² We cannot, however, determine the appropriateness of the indication for such placement. Differences in findings of the Computerized Registry of Patients With VTE (RIETE) and our study may partly arise from the fact that RIETE includes patients with VTE, whereas we restricted our attention to people with PE only.

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Clarification of Once-Daily Low-Molecular-Weight Heparin Dosing in Pulmonary Embolism

To the Editor:

We wish to clarify the dosing recommendations of low-molecular-weight heparin (LMWH) in the treatment of acute pulmonary embolism (PE) as discussed by Kearon et al¹ in an issue of *CHEST* (February 2012). According to Kearon et al,¹ American College of Chest Physicians (ACCP) Recommendation 5.4.2 states “in patients with acute PE treated with LMWH, we suggest once- over twice-daily administration.” The authors note that “this recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once-daily injection contains double the dose of each twice-daily injection).”¹ LMWH agents are pharmacokinetically dissimilar and, consequently, dosing approaches vary, as indicated by Garcia et al.² The dosing strategies of LMWHs used in the United States for treating acute PE are listed in Table 1.³ Noticeably, the approved daily regimen of enoxaparin does not equal “double the dose of each twice-daily injection.” Thus, should enoxaparin be included in this recommendation?

Throughout the ACCP guideline, seven comparative studies of various LMWH agents dosed once-daily for VTE are cited. Three included patients with PE; only one trial used daily enoxaparin.⁴ In this trial, patients with acute VTE were randomized to receive heparin or enoxaparin dosed at either 1 mg/kg bid or 1.5 mg/kg daily. Only 31.9% of the patients enrolled had PE at randomization; 94 of these patients received daily enoxaparin. There were no differences in recurrence of thromboembolism between the two dosing strategies in patients who had PE at baseline, but this trial was not adequately powered to assess this specific subgroup.

Given the wording of Recommendation 5.4.2 in Kearon et al,¹ many providers may inappropriately prescribe enoxaparin at 2 mg/kg daily or 1.5 mg/kg daily if they fail to read beyond the executive summary. Based on the cited studies, the authors did not intend for these doses to be used in the treatment of acute PE at all, but misinterpretation is likely if the reader is not vigilant. Such has occurred in our institution. A statement in the section regarding treatment of DVT clarifies that 2 mg/kg daily is not used, but this is not mentioned among the recommendations for treatment of PE.¹ The paucity of data for 1.5 mg/kg daily limits this dose as well.⁴

Table 1—LMWH Agents Available in the United States³

LMWH Agent	Typical Dosing for DVT or PE (Normal Renal Function)
Dalteparin ^a	DVT or PE: 200 units/kg daily or 100 units/kg bid
Enoxaparin	DVT: 1 mg/kg bid or 1.5 mg/kg daily; PE: 1 mg/kg bid
Tinzaparin	DVT with or without PE: 175 units/kg daily

LMWH = low-molecular-weight heparin; PE = pulmonary embolism.

^aTypical accepted dosing strategy. Dalteparin is not approved by the US Food and Drug Administration for acute VTE other than extended treatment of VTE in patients with cancer.

Enoxaparin is the top-selling LMWH in the United States.⁵ Its use is likely to increase with its recent generic approval. With the widespread use of enoxaparin, broad applications of inappropriate dosing strategies for PE could potentially increase hemorrhagic risks (2 mg/kg daily) or possibly embolic risks (1.5 mg/kg daily). We suggest that providers continue to dose enoxaparin bid for the treatment of acute PE.

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Response

To the Editor:

With this reply, we appreciate the opportunity to (1) reiterate the points made by Drs Miesner and Trewet, (2) identify that the question that they raise about treatment of pulmonary embolism also applies to the treatment of DVT (Recommendation 2.5.2), and (3) expand on our published explanation for the highlighted recommendations.¹ We identified five randomized trials that compared daily and bid regimens. In four of the five trials, patients in the two treatment groups received the

same total dose of low-molecular-weight heparin (LMWH) in a 24-h period (ie, each once-daily dose of LMWH had twice the number of units of LMWH as each of the bid doses). In the fifth trial by Merli et al,² the once-daily LMWH dose (ie, enoxaparin 1.5 mg/kg) was less than double each of the bid doses (ie, enoxaparin 1.0 mg/kg); therefore, the once-daily LMWH group received a lower total dose of LMWH over a 24-h period than the bid LMWH group.

As we noted, these trials provide low-quality evidence (hence, the grade C) that treatment of VTE (DVT or pulmonary embolism) with once-daily LMWH is associated with similar outcomes as treatment with bid LMWH. We judged the quality of evidence as low for two reasons. First, there is imprecision, as reflected by the wide 95% CI for the calculated risk ratios, and, consequently, we cannot exclude important differences in favor of either once-daily or bid LMWH. Second, there was an inconsistency of findings between the only two studies that assessed the effect on recurrent VTE at 3 months; one study appeared to favor the once-daily LMWH regimen (once-daily dose equal to the sum of the two bid doses),³ whereas the other (once-daily dose less than the sum of the two bid doses) favored the bid regimens.² The difference in dosing may have accounted for this inconsistency.

We made a weak recommendation (hence grade 2) in favor of once-daily LMWH over bid LMWH because (1) “we placed value on avoiding an extra injection per day” of LMWH and (2) the overall evidence suggested that once-daily regimens are as effective and safe as bid regimens. However, because recurrent VTE may have been higher with once-daily LMWH in the single study that treated patients with a lower 24-h total dose of LMWH in the once daily compared with the bid group, we only encourage (ie, express a preference for) once-daily regimens “when the approved once-daily regimen uses the same daily dose as the twice-daily regimen.”¹ We reinforce what Drs Miesner and Trewet have stated: It is not acceptable to treat VTE with enoxaparin 2.0 mg/kg once daily because this regimen has not been evaluated and is not approved for the treatment of DVT or pulmonary embolism.

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