VTE Prophylaxis After Hip Fracture Surgery

A number of agents are available that provide efficacy and safety for the prophylaxis of venous thromboembolism (VTE) in hip fracture patients, including low-molecular-weight heparins (LMWH), fondaparinux, and warfarin. The study by Comp and colleagues in the September issue (Comp P, Happe LE, Sarnes M, Farrelly E. Venous Thromboembolism Clinically Detected After Hip Fracture Surgery With Prophylaxis in a Clinical Practice Setting. *Am J Orthop*. 2008;37(9):470-475) sought to compare the incidence of clinically detected VTE associated with fondaparinux prophylaxis with the incidence associated with prophylaxis using either of 2 LMWHs or with unfractionated heparin.

I take issue with the methodology and the conclusions. In a retrospective cohort analysis of a database representing 500 hospitals, the authors note that their intent-to-treat approach assumes that the first agent a patient received was continued throughout and that the outcome is attributable to that initial agent. But very often the agent used in the hospital is changed when the patient is discharged. The study period encompassed the fracture surgery hospitalization plus 2 months of follow-up after discharge, or until in-hospital death. Moreover, when prophylaxis was started and stopped is unknown for each patient. There is a large selection bias present. All these factors will affect the rates of VTE.

Why include unfractionated heparin, which is not commonly used by orthopedic surgeons, and exclude warfarin, when warfarin and LMWH are the most commonly used pharmacologic agents? The effectiveness of pharmacologic agents outside the clinical trial setting is well known, as LMWH and warfarin have been in clinical use for over 20 years.

The value of this study is to once again bring to the attention of orthopedic surgeons the need for timely pharmacologic prophylaxis in this high-risk patient population. Prophylaxis should be started early, should be given to all patients, and should be continued for an appropriate length of time for each patient. A number of agents are available, and since all appear to be equally efficacious, other factors such as cost and safety need to be taken into account when choosing the most appropriate prophylaxis for each patient.

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Author's Disclosure Statement: Dr. Friedman wishes to note that he owns shares in Bayer and Johnson & Johnson, and he is a paid consultant to Boehringer-Ingelheim and Astellas Pharma, Inc., USA. He also wishes to note that he has an ongoing relationship with Sanofi-Aventis and Johnson & Johnson and receives research funding from Boehringer-Ingelheim, Astellas Pharma, Inc., USA, and Takeda.

Authors' Response

The authors of "Venous Thromboembolism Clinically Detected After Hip Fracture Surgery With Prophylaxis in a Clinical Practice Setting" (*Am J Orthop*. 2008;37(9):470-475) appreciate Dr. Friedman's commentary on our paper. We would like to respectfully clarify several important points raised by Dr. Friedman.

Dr. Friedman states that he takes issue with the methodology and conclusions of this paper. First, the authors would like to point out that the findings from this study are congruent with randomized clinical trial findings, which are typically considered the gold standard for comparisons. Specifically, in a trial of approximately 1,700 patients undergoing hip fracture surgery, fondaparinux 2.5 mg daily was associated with a 56% risk reduction in venous thromboembolism (VTE) prevention compared with enoxaparin 40 mg daily.[1] The results of our study substantiate these conclusions outside the rigors of a clinical trial setting.

The validity of the study period, which includes the initial hospitalization and a 2-month follow-up, is also questioned. This study time period closely mirrors the time frame examined in clinical trials, which assess the incidence of VTE day 11 and day 49.[1,2] Furthermore, the duration of treatment in our study (4.5 days) was also similar to the length of therapy in the clinical trials (4 to 9 days). Finally, it should be noted we present VTE from the inpatient period and the follow-up separately, and these data support the findings from the total time horizon.

Dr. Friedman also raises a valid question regarding the inclusion of unfractionated heparin (UFH) and the exclusion of warfarin as comparator groups. The 2008 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines state that low-dose UFH is an acceptable thromboprophylaxis agent following hip fracture surgery with an evidence level of Grade 1B.[3] In our sample, 12.5% of patients received UFH, which was more than the percentage who received fondaparinux (5.2%) or dalteparin (9.1%). While UFH may not be favored by orthopedic surgeons, it cannot be denied that it is used in this population. The authors recognize that warfarin

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is also used in this population (Grade 1B); however, we designed this study *a priori* to compare injectable anticoagulants on the basis that patients treated with injectables would have a more homogeneous risk profile versus those treated with oral agents.

Dr. Friedman correctly states a limitation of the intent-to-treat approach, in which we are unable to discern which therapeutic agent is employed in the outpatient setting. In our design, we assumed that rates of therapeutic change upon discharge would be minimal or equivalent across cohorts. Based on our experience within this field, we believe this assumption is tenable and not a significant confounder in the analysis.

We kindly thank Dr. Friedman for his assessment of this analysis; however, the extent of the limitations described does not attenuate the results of our study, particularly in light of congruence with previously published randomized clinical trial findings.

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