Differences Between Low-Molecular-Weight and Unfractionated Heparin for Venous Thromboembolism Prevention Following Ischemic Stroke*

A Metaanalysis

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Background: **Venous thromboembolism (VTE) remains a major cause of morbidity following stroke. The optimal form of pharmacologic prophylaxis following stroke is unknown.**
Methods: **We identified randomized trials comparing unfractionated heparin (UFH) to low-molecular-weight heparin (LMWH) for VTE prevention in ischemic stroke patients. We focused on the risk for VTE, pulmonary embolism (PE), bleeding, and mortality as a function of the type of agent used for prophylaxis. Findings were pooled with a random-effects model.**
Results: **We identified three trials including 2,028 patients. Two of the studies were blinded, two studies relied on enoxaparin, while one study utilized certoparin. In two studies, UFH was administered three times a day, while it was administered twice daily in the remaining study. The use of LMWH was associated with a significant risk reduction for any VTE (odds ratio [OR], 0.54; 95% confidence interval [CI], 0.41 to 0.70; $p < 0.001$). Limiting the analysis to proximal VTEs also indicated that LMWHs were superior (OR with LMWH vs UFH, 0.53; 95% CI, 0.37 to 0.75; $p < 0.001$). LMWH use led to fewer PEs as well (OR, 0.26; 95% CI, 0.07 to 0.95; $p = 0.042$). There were no differences in rates of overall bleeding, intracranial hemorrhage, or mortality based on the type of agent employed. Restricting the analysis to the reports employing enoxaparin did not alter our findings.**
Conclusions: **The prophylactic use of LMWH compared to UFH following ischemic stroke is associated with a reduction in both VTE and PE. This benefit is not associated with an increased incidence of bleeding. Broader use of LMWH for VTE prevention after ischemic stroke is warranted.** ***(CHEST 2008; 133:149–155)***

Key words: deep vein thrombosis; heparin; low-molecular-weight heparin; prevention; pulmonary embolism; stroke

Abbreviations: CI = confidence interval; CVA = cardiovascular accident; df = degree of freedom; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; NIH = National Institutes of Health; OR = odds ratio; PE = pulmonary embolism; UFH = unfractionated heparin; VTE = venous thromboembolism

Venous thromboembolism (VTE), consisting of both deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a major focus for preventive efforts in hospitalized patients. VTE is associated with substantial morbidity, and PE, in particular, can be fatal. In addition, VTE developing in persons admitted to the hospital for other reasons prolongs hospitalization and increases hospital costs.[1] Some studies[1,2] have estimated that the costs for caring for such DVTs and PEs approach $5,000 and $15,000 per case, respectively. Because of these facts, many formal guidelines[2,3] exist to aid clinicians in making decisions regarding VTE prevention. Underscoring the importance of VTE prevention, federal organizations now audit hospital compliance with select VTE prevention measures.

Patients who have suffered ischemic strokes (*ie*, cerebrovascular accidents [CVAs]) face a heightened

VTE risk.[4] The immobility accompanying ischemic CVA increases the potential for VTE. The underlying diseases that contribute to an individual's CVA may also enhance the possibility of VTE, as can the general proinflammatory state accompanying CVA. Screening studies performed in CVA patients prior to the era of routine prophylaxis have suggested that the prevalence of VTE may approach 70%.[4] More strikingly, 1 to 2% of persons with hemiplegia after a CVA experience a fatal PE.[4,5]

Unfortunately, the optimal form of VTE prophylaxis following CVA remains unknown. A 2004 meta-analysis[6] questioned the value of nonpharmacologic measures. Studies[6] comparing some form of heparin to placebo have indicated that these agents offer benefits in terms of VTE risk reduction. In a number of settings,[7,8] low-molecular-weight heparins (LMWHs) have emerged as an attractive alternative to unfractionated heparin (UFH). Few trials, however, have directly compared UFH to LMWH for VTE prevention following ischemic CVA. One major concern in CVA patients is the potential for bleeding associated with exposure to any form of anticoagulant. The relative risk for bleeding with the use of either UFH or LMWH in ischemic CVA patients also remains undefined, and earlier studies may have been underpowered to assess this concern.

We hypothesized that LMWH would prove superior to UFH for VTE prevention following ischemic stroke. We also theorized that the potential for major bleeding with these anticoagulants in the setting of recent stroke would be similar. To evaluate our hypotheses, we conducted a metaanalysis exploring studies comparing LMWH to UFH for VTE prevention following ischemic CVA.

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Materials and Methods

Search Strategy

We searched MEDLINE (1966 to April 2006), EMBASE (January 1990 to April 2006), the Cochrane Library, and clinicaltrials.gov to identify prospective, randomized trials of LWMH and UFH for VTE prevention in ischemic stroke patients. The following key words were utilized: "deep vein thrombosis"; "heparin"; "ischemic"; "low-molecular weight heparin"; "prevention"; "prophylaxis"; "pulmonary embolism"; "stroke"; "unfractionated"; and "venous thromboembolism." We also hand searched the abstracts from the annual meetings of the American Academy of Neurology, the American College of Chest Physicians, the American Heart Association, the American Society of Hematology, the American Thoracic Society, and the International Society of Thrombosis and Hemostasis from 2001 to 2006. We reviewed the references of the selected articles and contacted experts in the field. We had no language restrictions, and the search was conducted in duplicate.

We excluded trials that compared a form of heparin (either UFH to LMWH) to placebo. We additionally excluded studies in which heparin was administered as part of the treatment paradigm for ischemic CVA management and not expressly for VTE prevention, and eliminated from review reports in which VTE was not the primary end point. Nonrandomized studies were not included in our analysis. Two investigators examined potentially relevant articles and abstracts independently to ensure that they met our inclusion criteria.

Study Evaluation and Data Extraction

Because no objective tools exist for assessing the quality of randomized studies of VTE prophylaxis, two investigators independently rated the quality of the randomized trials included in this review using the scoring system created by Jadad et al.[9] These two investigators also independently extracted the relevant data in duplicate. Specifically, we collected information dealing with the severity of illness of the patients studied, the forms of heparin utilized, the frequency of their dosing, and the methods used for the diagnosis of VTE. VTE served as the primary end point and was also separated into its component pieces, DVT and PE. Rates of bleeding, both intracerebral bleeds and extracranial major hemorrhage, were also recorded. To evaluate safety, we collected information on mortality and the frequency of and diagnostic criteria for heparin-induced thrombocytopenia.

Sensitivity Analysis

Given the potential for pharmacokinetic differences between various types of LMWHs, we were concerned that LMWHs may not be interchangeable with respect to their effects on either VTE or bleeding. Therefore, *a priori*, we decided to conduct specific sensitivity analyses as a function of the type of LMWH utilized. In other words, we completed a series of analyses pooling trials only utilizing the same LMWH vs UFH in order to explore whether this altered our overall findings.

Statistical Analysis

To assess for the potential for publication bias to alter our findings, we created funnel plots and calculated the Begg statistic. Agreement between the two investigators in their quality ratings of the clinical trials was compared with the κ statistic. To summarize the effect of LMWH and UFH on rates of VTE and bleeding, we relied on the risk differences as computed based on