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LETTER

Mortality as Primary End Point in Studies of Heparin Thromboprophylaxis

To the Editor:

I read with interest Lederle and colleagues'[1] article on prophylaxis of thromboembolism. The authors raise some interesting points regarding the lack of hard evidence supporting pharmacoprophylaxis of venous thromboembolism (VTE) with heparin in medical patients. However, I disagree with the authors' suggestion that total mortality remains the best measure for evaluating the effectiveness of heparin prophylaxis.

Although death from fatal pulmonary embolism remains the most dramatic manifestation of VTE, I suggest that the morbidity from nonfatal pulmonary embolism and deep vein thrombosis (which includes the serious and chronic medical conditions of pulmonary hypertension and postphlebitic syndrome) is of much greater import when evaluating the effectiveness of pharmacoprophylaxis.

In an article published in 2000, Goldhaber et al[2] looked at consecutive cases of VTE at their institution and found 14 deaths attributed to VTE. Twelve of 14 of those patients who died of VTE were critically ill, had cancer, or had spinal cord injuries. If we accept Goldhaber and colleagues' data (which is consistent with my own experience) as an accurate reflection of those patients who die of VTE in the hospital, by advocating total mortality as the best measure for evaluating the effectiveness of heparin prophylaxis, Lederle et al[1] are selecting a unique patient population (ie, the very sick) to evaluate. Mortality as a primary end point makes studying a less sick population difficult (as the authors discovered). It also results in placing a high value on preventing a fatal pulmonary embolism in a patient with a terminal illness or serious comorbidities and discounts the prevention of a nonfatal VTE event (with its potential lifelong and serious complications of pulmonary hypertension and postphlebitic syndrome) in a person with an extended and high-quality life expectancy.

Although Lederle et al[1] correctly point out that none of the properly randomized trials that they reference in their article demonstrated a mortality benefit with heparin prophylaxis, it is important to point out that only 1 was designed or powered to do so. Further, in this 1 study with more than 11,000 patients, Gardlund[3] noted a 40% reduction in nonfatal thromboembolic events ($P = .0012$). Although Gardlund notes methodologic concerns and regards these secondary end point data as "inconclusive," I do not think Lederle et al should fully discount them. As a pragmatic matter, given the robust relative risk reduction and "*P* value" combined with the relative safety and low expense of low-dose unfractionated heparin, it is hard to ignore this potential benefit.

In contrast with the authors, I believe that current guidelines[4] recommending heparin prophylaxis in selected medical patients are an appropriate reflection of the available scientific data, cost, safety, and efficacy.

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