

Editorial Focus

Anticoagulants for thrombosis prophylaxis following surgery: A continuing saga

Joseph A. Caprini

Department of Surgery, Evanston Northwestern Healthcare, Skokie, Illinois, USA

More than 30 years ago the landmark multicenter trial from 28 medical centers demonstrated in 4,000 patients that the administration of small doses of unfractionated heparin (UFH) to surgical patients reduced the deep vein thrombosis (DVT) rate from 24.6% in the placebo group to 7.7% in the heparin arm with a corresponding reduction in fatal pulmonary emboli from 0.8% to 0.1% (1). Even more remarkable was the meta-analysis by Collins 13 years later involving more than 13,000 patients from 70 medical centers that reaffirmed the original multicenter trial results. The incidence of DVT was reduced from 22.4% to 9.0% by administration of small doses of UFH in general, gynecologic, orthopedic, and urologic surgery patients. Again the incidence of fatal pulmonary embolism (PE) was reduced from 0.9% in the control group to 0.3% in the heparin group (2).

Seventeen years later Hass et al. reported the results of a randomized, double-blind comparison of UFH and low-molecular-weight heparin (LMWH) in 23,078 surgical patients which demonstrated that the fatal PE incidence in either group was 0.15% (3).

Over the years multiple consensus conferences have concluded that high-risk patients having surgical operations should be protected by anticoagulants. The latest consensus guidelines indicate that the incidence of DVT without prophylaxis is 40–80% and the fatal PE rate is as high as 5% in some of these patients without prophylaxis (4–6). One would assume that after all these years and in light of overwhelming evidence from around the world prophylaxis would be uniformly administered to high-risk surgical patients. Recently the results of a registry of 30,827 surgical patients revealed that 64% of these individuals were at risk for developing venous thromboembolism (VTE) and only a disappointing 59% received appropriate thrombosis prophylaxis (7). This observer wonders what additional evidence is necessary to convince physicians to protect their high-risk patients.

The problem has been compounded in this era of outpatient and laparoscopic surgery that may markedly shorten hospital stay. High-risk patients may be given prophylaxis before and

after the surgical procedure, but it is rarely continued for the full seven days if earlier discharge has occurred. All of the above studies in thousands of patients have included a 7–10 day treatment period. There are no data to suggest that shortening the period of prophylaxis is justified. Cancer patients in particular may not have resumed normal mobility and may spend considerable time in the recliner resting from their operation. Often they are taking narcotics for pain control and may have indwelling lines for chemotherapy, antibiotics for ongoing infection, etc. These patients remain at risk and, while no randomized trials have been done, there is evidence from several studies that out-of-hospital prophylaxis is necessary.

One study involving 28,953 patients documented 90 patients with symptomatic PE during their hospital stay. Within 30 days of hospital discharge, 29 patients were readmitted because of PE and the delayed embolic events were seen a median of six days after discharge and 18 days after surgery. A number of these patients had low-risk surgical procedures. The authors suggested that post-discharge prophylaxis may be important in some surgical patients (8). Fourteen years later the incidence of clinical VTE in 1,238 patients undergoing operations for cancer was 2.1%. Forty percent of the thromboembolic events occurred more than three weeks postoperatively. In-hospital prophylaxis was given in 81.6% and post-discharge prophylaxis in 30.7% of the patients. The authors conclude that “VTE remains a common complication of cancer surgery, with a remarkable proportion of events occurring late after surgery. In patients undergoing cancer surgery, VTE is the most common cause of death at 30 days after surgery” (9). An incidence-based model by Heit et al. (10) estimated that 613,423 non-fatal VTE events occur annually and 296,370 fatal VTE events in a given year in the US. It was estimated that of these totals 193,598 non-fatal VTE and 106,550 fatal VTE occurred out-of-hospital. The authors emphasized the importance of these findings, particularly the events occurring in the community (10).

The study by Bottaro et al. (11) in this issue of the *Thrombosis and Haemostasis* is a meta-analysis of three clinical studies that compare the efficacy and safety of extended LMWH pro-

Correspondence to:
Dr. Joseph A. Caprini
Department of Surgery, Evanston Northwestern Healthcare
9977 Woods Drive, Skokie, IL 60077, USA
Tel.: +1 847 663 8050, Fax: +1 847 663 8054
E-mail: j-caprini@northwestern.edu

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phylaxis following abdominal surgical operations for cancer. These studies were selected from 787 articles screened for the strict inclusion/exclusion criteria which required a randomized prospective design, at least 21 days of postoperative LMWH and appropriate venographic endpoints at 30 days. An adequate description of all bleedings endpoints and all-cause mortality was a further requirement. The results showed a statistically significant reduction in the VTE incidence from 13.6% in the short-term prophylaxis group to 5.93% in the extended prophylaxis group. Similar significant reductions in DVT and proximal DVT were also seen. There was no significant difference in major or

minor bleeding between the two groups. The authors conclude that extended prophylaxis is a safe and effective strategy for VTE prevention following high-risk abdominal surgery.

This report is well done and represents a logical extension of a great deal of previous research in the VTE arena. I am sure that before this approach is widely adopted further studies especially in cancer patients will need to be completed. Even then I am skeptical that this approach will be extensively used given the dismal past history of physician compliance with evidence-based guidelines.

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