

# How long should venous thromboprophylaxis be given following cancer surgery?

Bergqvist D, Agnelli G, Cohen AT, Eldor A, Nilsson PE, Le Moigne-Amrani A, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. *N Engl J Med* 2002;346(13):975-80.

**Background:** Patients undergoing abdominal surgery for cancer are at high risk of postoperative venous thromboembolism (VTE). Although the traditional approach has been to administer heparin subcutaneously only during their hospital stay, patients are known to remain at risk of VTE for up to several weeks postoperatively. More prolonged courses of thromboprophylaxis have been shown to reduce the incidence of VTE in other patients, such as those who have undergone arthroplasty of the lower limb.<sup>1</sup> Whether such an approach would confer similar benefit to cancer patients is unknown.

**Question:** In patients undergoing abdominal or pelvic surgery for cancer, does a 3-week course of prophylaxis with enoxaparin prescribed beyond the first 6 to 10 postoperative days reduce the risk of VTE without increasing the risk of hemorrhage?

**Design:** This multicentre, prospective, double-blind, randomized controlled trial involved patients 40 years of age or older who were undergoing elective abdominal or pelvic surgery with curative intent for cancer of the gastrointestinal or genitourinary tracts or cancer of female reproductive organs. All patients were treated with enoxaparin (40 mg once daily) for 6–10 days postoperatively and were then randomly assigned to receive either placebo or enoxaparin (40 mg once daily) for an additional 19–21 days.

To ascertain the incidence of postoperative VTE, venography of the lower limbs was performed routinely within 3 days after completion of the additional course of treatment. Results were interpreted by a central committee unaware

of treatment allocation. Any symptoms suggestive of VTE occurring before the scheduled venography were assessed with appropriate objective testing, the results of which were also adjudicated by the central committee.

The primary efficacy end point was the incidence of VTE at the conclusion of the additional course of treatment. Safety was assessed by determining the incidence of hemorrhage during the same period. Patients were also followed for 3 months after surgery for the occurrence of death, VTE, hemorrhage or other adverse events.

**Results:** Between October 1998 and June 2000, 501 patients were randomly assigned to receive enoxaparin ( $n = 253$ ) or placebo ( $n = 248$ ) for a mean duration of 19.3 and 19.5 days respectively. This followed 6–10 days of open-label treatment with enoxaparin. Venography could not be performed or the results could not be interpreted in 81 placebo cases and 88 enoxaparin cases; these patients were excluded from the efficacy analysis. Of the remaining 332 patients, members of the placebo ( $n = 167$ ) and enoxaparin ( $n = 165$ ) groups were comparable with respect to age, sex, body mass index and risk factors for VTE.

By the end of the prolonged treatment period the overall incidence of VTE was 8.4% (28/332). The incidence was 12.0% (20/167) in the placebo group and 4.8% (8/165) in the enoxaparin group ( $p = 0.02$ ), for a relative risk reduction of 60% (95% confidence interval 10%–82%) and an absolute risk reduction of 7.2% (number needed to treat = 14). In all but one instance, VTE was diagnosed on routine venography; one episode of pulmonary embolism was diagnosed when a patient presented with symptoms before the end of the treatment period. Of the 28 cases of deep vein thrombosis detected, only 4 were proximal (3 in the placebo group, 1 in the enoxaparin group).

All 501 patients were included in the safety analysis. At the end of the treatment period, the incidence of hemorrhage did not differ significantly between the groups (3.6% in the placebo group and 5.1% in the enoxaparin group,  $p = 0.51$ ). Although no patients died during the treatment period, 9 (6 in the placebo group and 3 in the enoxaparin group) died during the 3-month follow-up period. The only death attributed to VTE occurred in a patient who had been given placebo.

**Commentary:** This study adds to the body of evidence that cancer patients remain at risk of postoperative VTE for several weeks after surgery. The study also shows, however, that most of the patients with VTE had distal deep vein thrombosis — a condition associated with low morbidity and mortality.

**Practice implications:** An additional 19–21 days of enoxaparin prophylaxis reduces the incidence of VTE in patients undergoing abdominal or pelvic surgery for cancer. Given that most of the events prevented were distal deep vein thrombosis, further research is required to determine whether prolonged prophylaxis offers any advantage over a strategy of close surveillance (e.g., with serial venous ultrasonography) and prompt treatment of clinically significant episodes of VTE.

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## Reference

- Dahl O, Andreassen G, Aspelin T, Muller C, Mathiesen P, Nyhus S, et al. Prolonged thromboprophylaxis following hip replacement surgery — results of a double-blind, prospective, randomised, placebo-controlled study with dalteparin (Fragmin). *Thromb Haemost* 1997;77:26-31.