

CIHR/CMAJ: TOP ACHIEVEMENTS IN HEALTH RESEARCH

Essay for the CIHR/CMAJ award: the role of low-molecular-weight heparin therapy venous thromboembolism

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Russell Hull, the POISE-1 investigators, and Cyril Frank and colleagues for the Alberta Bone and Joint Health Institute are the highest-ranking winners of the 2009–2010 CIHR/CMAJ competition for the Top Achievements in Health Research. Dr. Hull describes his work in treatments for venous thrombosis in the following essay. The essay by Dr. Devereaux and colleagues, the essay by Dr. Frank and colleagues, and synopses of the other three winning achievements are available at cmaj.ca.

There is a need for an effective and safe alternative to therapy with vitamin K antagonists in a broad spectrum of patients with venous thrombosis. Long-term use of low-molecular-weight heparin, although administered subcutaneously, may be a viable option. A key concern with long-term use of vitamin K antagonists is harm resulting from hemorrhagic complications. Aggregate data reported in a systematic review identified that long-term use of low-molecular-weight heparin may cause less bleeding, but the authors cautioned that further study was needed in individual trial settings to determine where safety was improved.¹ These authors also reported uncertainty on the efficacy of long-term use of low-molecular-weight heparin for preventing recurrent venous thromboembolism, but they noted that the doses used in some trials may have resulted in inadequate therapy.¹

Research evaluating the treatment of deep vein thrombosis with low-molecular-weight heparin that had shown a reduction in mortality among patients with cancer led to renewed interest in the effect of these agents on the survival of such patients.² Randomized trials were needed to investigate the effectiveness and safety of the long-term use of low-molecular-weight heparin therapy for patients with both venous thromboembolism and cancer.

Development of the program

Under the auspices of the Medical Research Counsel (now the Canadian Institutes of Health Research [CIHR]) and with an operating grant for industry-partnered collaborative research, a multicentre randomized clinical trial program was initiated in 1994 to address the substantive clinical need for an alternate to vitamin K antagonist therapy, particularly among patients with cancer who also required treatment for venous thromboembolism.

When this research program was launched, there were no data available from randomized controlled trials evaluating long-term therapy with low-molecular-weight heparin versus vitamin K antagonist therapy. The clinical need for such a research program was based on the initial results from studies that showed long-term use of low-molecular-weight heparin among patients with venous thromboembolism was associated with a reduction in cancer mortality.²

The findings of the clinical trial program are reported by Hull and colleagues in three papers published in the *American Journal of Medicine*.^{3–5} In summary, 737 patients were enrolled in a multi-

Competing interests:

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KEY POINTS

- A substantial clinical need exists for an alternate to vitamin K antagonist therapy for treating deep vein thrombosis in many patients with and without cancer
- In a broad spectrum of patients, low-molecular-weight heparin therapy has been shown to be as effective as, and less harmful than, treatment with vitamin K antagonists.
- In patients with cancer who have venous thromboembolism, long-term use of low-molecular-weight heparin is as safe as, and more effective than, vitamin K antagonist therapy for preventing recurrent venous thromboembolism.
- Research evaluating the effectiveness of low-molecular-weight heparin as an adjunctive therapy for improving survival among patients with advanced cancers is currently underway.

centre, randomized, open-label clinical trial using objective outcome measures for both efficacy and safety that compared therapies (tinzaparin or usual care) for three months.⁴ The patients were divided into two groups: patients without cancer who required long-term treatment for venous thromboembolism, and patients with cancer who required long-term treatment for venous thromboembolism. The patients with cancer were stratified separately at the time of randomization. Outcomes were assessed at 3 and 12 months.

Key findings

Of the 369 patients receiving tinzaparin, 18 (4.9%) had recurrent venous thromboembolism at three months, compared with 21 (5.7%) of the 368 patients receiving usual care (absolute difference -0.8%, 95% confidence interval [CI] -4.1 to 2.4). Hemorrhagic complications, using the definitions endorsed by the International Society on Thrombosis and Hemostasis⁶ and developed by Hull and coworkers in 1982,⁷ occurred less often in the low-molecular-weight heparin group, largely because of a lower incidence of minor bleeding. Forty-eight of the 369 patients (13%) in the low-molecular-weight heparin group had bleeding versus 73 (19.8%) of the 368 patients receiving usual anticoagulation therapy (absolute difference -6.8%, $p = 0.011$; risk ratio = 0.66). New major bleeding events ended early (by day 23, $p = 0.034$) for patients receiving low-molecular-weight heparin, but such events persisted throughout the study for patients receiving vitamin K antagonists. Mortality was not significantly different between therapy groups.

This study showed that the effectiveness of low-molecular-weight heparin is similar to that of vitamin K antagonists for preventing recurrent venous thromboembolism in a broad spectrum of patients. However, low-molecular-weight heparin therapy causes less harm than the vitamin K antagonist, thus expanding the therapeutic options for patients with proximal deep vein thrombosis. These results suggest the possibility of a broader role for long-term treatment with low-molecular-weight heparin in selected patients.

A prospective evaluation of patients with cancer and proximal venous thrombosis was also done, as patients with cancer were randomized separately within the overall population. This allowed us to study the effectiveness and safety of long-term use of low-molecular-weight heparin specifically for this population.³ Of 200 patients in this group, 100 received tinzaparin and 100 received usual care. At 12 months, 16 of 100 patients receiving usual care had recurrent thromboembolism, versus 7 of 100 patients

receiving low-molecular-weight heparin ($p = 0.044$; risk ratio = 0.44; absolute difference -9.0, 95% CI -21.7 to -0.7). Bleeding, largely minor, occurred in 27 of the patients receiving tinzaparin and in 24 of the patients receiving usual care (absolute difference -3.0, 95% CI -9.1 to 15.1).

Among patients without additional risk factors for bleeding at the time of randomization, major bleeding occurred in none of the 51 patients receiving tinzaparin and in only 1 (2.1%) of the 48 patients receiving usual care. The high mortality at one year reflected the severity of the cancers; 47% of the patients in each group died. These findings confirmed the limited, but benchmarked, data in the literature that had been reported during the conduct, analysis and reporting phase of our trial (e.g., Lee and colleagues⁸) and showed that low-molecular-weight heparin is more effective than vitamin K antagonist therapy for preventing recurrent venous thromboembolism in patients with both cancer and proximal venous thrombosis.

Impact of the program

Based on the earlier findings of Hull and colleagues,^{9,10} Lee and colleagues⁸ and Buller and colleagues¹¹ concluded that the evidence supported the use of low-molecular-weight heparin for at least the first three to six months of long-term treatment for most patients with deep vein thrombosis and cancer (Grade 1A). Subsequently, the 2008 report by the 8th American College of Chest Physicians' Conference on Antithrombotic and Thrombolytic Therapy (reported by Kearon and colleagues)¹² recommended use of low-molecular-weight heparin as the long-term treatment of choice in patients with cancer and deep vein thrombosis (Grade 1A).

The American College of Chest Physicians' recommendations^{11,12} have resulted in widespread use of long-term low-molecular-weight heparin therapy in patients with venous thromboembolism and cancer. This therapy has also been endorsed in a guideline by the American Society of Clinical Oncology,¹³ which reported and cited the CIHR-supported data, and by several international guidelines.¹⁴⁻¹⁶ The recommendations made in these consensus guidelines are widely accepted.

Future directions

Continued research using randomized clinical trials is underway to evaluate the potential benefit that low-molecular-weight heparin therapy may have on mortality among patients with cancer but without deep vein thrombosis. Because aggregate

data suggest that low-molecular-weight heparin may act as an adjunct and modify the natural history of cancer, additional research has been started to evaluate the impact of this therapy as an adjunct in the treatment of patients with malignancy.

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