Economic Evaluation of Outpatient Treatment With Low-Molecular-Weight Heparin for Proximal Vein Thrombosis

**Background:** The safety and efficacy of taking low-molecular-weight heparin at home was previously demonstrated in a clinical trial in which patients with acute proximal deep vein thrombosis were randomized to receive either intravenous standard heparin in the hospital or subcutaneous low-molecular-weight heparin administered primarily at home. Treatment in the home has the potential to substantially reduce the cost to the health care system.

**Methods:** To conduct an economic evaluation we prospectively collected data on resource use and health-related quality of life (Medical Outcomes Study Short-Form 36) on the 300 patients who formed the trial stratum presenting with proximal vein thrombosis as outpatients, of whom 151 received standard heparin and 149 received low-molecular-weight heparin. The primary viewpoint of the analysis was societal, and costs included health care costs, patient travel costs, and productivity costs as a result of time off work. Costs were assessed over a period of 3 months from randomization. Quality of life was assessed as the change in Short-Form 36 domain scores from baseline to day 7 for each treatment group. All costs are reported in 1997 Canadian dollars.

**Results:** There were 11 recurrent thromboembolic events and 1 bleed in the 151 patients who received standard heparin; the corresponding data for the 149 patients receiving low-molecular-weight heparin were 10 and 4, respectively. The mean cost per patient who received standard heparin was Can $5323 compared with Can $2278 for low-molecular-weight heparin, a total societal cost savings per patient using low-molecular-weight heparin of Can $3045 (95% confidence interval, Can $2012-$4050). There was no difference in quality of life between the 2 groups except for the domain of social functioning, where a greater improvement from baseline to day 7 was observed for the low-molecular-weight heparin group vs the standard heparin group (P = .005).

**Conclusions:** For patients with acute proximal deep vein thrombosis, treatment at home with low-molecular-weight heparin is less costly than hospital-based treatment with standard heparin. The economic evidence in favor of outpatient treatment with low-molecular-weight heparin exhibits dominance; a situation of reduced cost is created with no compromise in clinical outcomes or patients’ quality of life.
PATIENTS AND METHODS

TRIAL DESIGN

Patients with symptomatic acute proximal deep vein thrombosis diagnosed by either venography or duplex ultrasonography were assigned treatment with either low-molecular-weight heparin primarily at home or continuous intravenous standard heparin in the hospital. Several three categories of patients were entered: those who presented as outpatients (n = 300); patients with deep vein thrombosis admitted at night or on a weekend who, for logistic reasons, could not be enrolled in the study immediately and thus were first treated with standard heparin (n = 157); and patients who were hospitalized for other reasons, such as surgery, and in whom deep vein thrombosis was subsequently diagnosed (n = 43).

The patients assigned to therapy with low-molecular-weight heparin received 1 mg of enoxaparin sodium (Rhône-Pou当地的) per kilogram of body weight subcutaneously twice daily. The patients assigned to therapy with standard heparin were admitted to the hospital and received a bolus dose of 5000 U intravenously followed by a continuous infusion of 20,000 U of standard heparin in 500 mL of 5% dextrose solution administered at 32 mL/h. The dose rate was adjusted to maintain the activated partial thromboplastin time within a targeted range of 60 to 85 seconds. The patients began to receive warfarin sodium on the evening of the second day of treatment with the study medication. The prothrombin time was performed daily. The warfarin was prescribed to achieve an international normalized ratio of 2.0:3.0. In the outpatients, the prothrombin time was measured daily at the outpatient hospital laboratory, a community laboratory, or the patient’s home by a staff member of a community laboratory. The study medication was discontinued when the targeted therapeutic range for the international normalized ratio was reached and maintained for 2 consecutive days. Each patient was treated for at least 5 days with either low-molecular-weight heparin or standard heparin. All patients were scheduled to receive warfarin for at least 3 months.

The principal outcome events in this trial were symptomatic recurrent venous thromboembolism within 90 days after randomization and bleeding during the period of administration of study medication (or within 48 hours after its discontinuation). The criteria used to define these outcomes have been described previously. The study protocol was approved by the institutional review boards of the participating clinical centers. Informed consent was obtained from eligible patients before their assignment to a study treatment.

ECONOMIC HYPOTHESES

For the economic evaluation, we elected to study only the first stratum of patients who presented as outpatients; of these 300 patients, 151 were randomized to receive standard heparin in the hospital, and 149 to receive low-molecular-weight heparin at home. Hence we restricted our focus to an economic evaluation of a clinical strategy in which persons presenting with proximal deep vein thrombosis as outpatients would be treated as outpatients with low-molecular-weight heparin instead of the current practice of admitting them to the hospital for treatment with standard heparin. Twenty-nine of the patients receiving low-molecular-weight heparin in this stratum were admitted for a short time to learn how to self-inject the study medication.

Our economic hypotheses were 2-fold: (1) that the mean cost per patient randomized to home treatment with low-molecular-weight heparin would be lower than that of patients randomized to standard heparin; and (2) that there would be no difference between treatment groups in health-related quality of life during the 7 days following randomization. In summary, we hypothesized that low-molecular-weight heparin treatment would be dominant over standard heparin, as it reduces costs without compromising clinical effectiveness or health-related quality of life.

VIEWPOINT AND TIME HORIZON

Consistent with current guidelines, the primary viewpoint of our analysis was societal, including costs to the health care system, travel costs for patients, and costs to society arising from patients’ and/or caregivers’ absence from work and lost productivity. The time frame for the study was the sum of 2 periods: the heparin treatment period of approximately 7 to 10 days following randomization and the warfarin treatment period of 3 months. We included all events and suspected events for the heparin period (for bleeding events up to 48 hours following discontinuation of heparin treatment). In the warfarin period we included only recurrent or suspected episodes of deep vein thrombosis or pulmonary embolism; suspected bleeding events were excluded because these would not be plausibly attributable to the initial heparin regimen.

COLLECTION OF DATA ON RESOURCES USED

Resources used by patients in both treatment groups were recorded prospectively on case report forms by study nurses. Health care costs fell into 2 categories: scheduled treatment costs, which arose from the initial and planned therapy and its routine monitoring, and nonscheduled investigation and treatment costs, which were resources used as a consequence of patients presenting with suspected clinical events during the follow-up period. Under scheduled treatment costs, data were collected on drugs and their administration, including costs of nursing time to train patients for self-injection with low-molecular-weight heparin, days in the hospital, visits to outpatient thrombosis clinics, use of monitoring tests or other investigations following randomization, and home visits from nurses. We excluded the costs of warfarin during the warfarin-only period because this was common to both treatment groups.

Nonscheduled resource use was that arising for patients with a suspected deep vein thrombosis, pulmonary embolism, or bleed; in such cases a cost case report form was completed, which gave details of studies such as venography, ultrasonography, and lung scans, and also outlined the treatment given. In addition to suspected

Continued on next page
clinical events, nonscheduled resource use was assessed for patients who returned to the center with symptoms, problems, or questions arising from their treatment or disease that did not result in clinical suspicion of events but did use resources. A committee adjudicated whether each of these latter contacts with the health care system was likely related to the disease or its management. This committee was blind to treatment assignment and had predetermined criteria to determine whether events were related to the study. If an event consisted of clinical symptoms or signs of deep vein thrombosis or pulmonary embolism, then the event was included in the analysis. If during the postheparin period, a visit was related to the monitoring of warfarin or a bleed during warfarin therapy, then the event was not included.

For the combined heparin and warfarin treatment periods, days lost from work by patients or caregivers were recorded to estimate productivity losses. For the heparin period only, patients reported kilometers traveled associated with therapy to permit calculation of travel costs.

DATA SOURCES FOR UNIT COSTS

Acquisition costs of standard heparin and warfarin were obtained from 2 hospital pharmacies in Hamilton, Ontario. The current Canadian market price for low-molecular-weight heparin (enoxaparin) of Can $0.20 per mL was used in the analysis. Relevant price weights for hospital resources were estimated using data from a fully allocated, patient-level, itemized costing system known as the Ontario Case Costing Project. This system is available in a number of Ontario hospitals; data for this study were obtained from a large teaching hospital in southeast Ontario for days in intensive care, days on a ward, cost of clinic visits, laboratory tests, diagnostic interventions, and emergency department visits. The cost of physician services was evaluated using appropriate fees from the Ontario Health Insurance Plan Schedule of Benefits. The cost of nurse home visits was based on average cost per visit from home care programs in the Toronto, Ontario area. The cost of work absence was evaluated using the industrial average wage rate for Ontario. Travel cost was estimated at the McMaster University reimbursement rate of Can $0.35 per kilometer. All costs are reported as 1997 Canadian dollars (multiplication by 0.7 provides approximate US dollar values at current exchange rates).

data for the economic analysis were collected prospectively during the trial. In addition, this report presents a comparison of the health-related quality of life between treatment groups.

RESULTS

CLINICAL AND COST EVENTS

There were 59 suspected clinical events among the 151 patients randomized to standard heparin, compared with 56 events among the 149 patients receiving low-molecular-weight heparin, a difference that was not statistically significant (P = .88, Table 1). Furthermore, of these suspected events there was no significant difference in the number of confirmed thromboembolic events or bleeds between the 2 treatment groups. Therefore, the results for the outpatient stratum are consistent with the main clinical trial for all strata combined: there is no statistically significant difference in safety or efficacy between the 2 treatment groups.

UNIT COSTS AND USE OF RESOURCES

For each of the resource items collected, unit costs and the mean number of resources used per patient by treatment groups are given in Table 2. Patients assigned to standard heparin spent an average of 6.7 days in the hospital compared with 0.9 days for per-
sons assigned to low-molecular-weight heparin, at a
daily cost of Can $487 on a ward before the addition
of any procedures, tests, or time in intensive care.
Consistent with the clinical evidence of no difference
in the rate of clinical events, there were 17 nonsched-
uled hospital admissions in the standard heparin
group compared with 19 in the low-molecular-weight
heparin group. Patients (or their caregivers) receiving
standard heparin had a mean of 6.79 days off work vs
3.14 days for patients receiving low-molecular-weight
heparin treatment during the combined period of hep-
arin and warfarin treatment. Patient travel during the
heparin treatment period was higher for the low
molecular-weight heparin group at 89.9 km vs 0.7 km
for the standard heparin group.

Table 1. Suspected Clinical Events and Other Cost Events

<table>
<thead>
<tr>
<th>Events</th>
<th>Standard Heparin (n = 151)</th>
<th>LMWH (n = 149)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected clinical events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed: DVT</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bleed during heparin period</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bleed during warfarin sodium period (excluded)</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Not confirmed: DVT</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Bleed during heparin period</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Bleed during warfarin period (excluded)</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Other cost events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly or probably related to DVT and/or bleed</td>
<td>6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Not related to DVT and/or bleed (excluded)</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*LMWH indicates low-molecular-weight heparin; DVT, deep vein thrombosis. Unless otherwise indicated, data are given as number of patients.

Table 2. Unit Costs and Mean Use of Health Care and Other Resources

<table>
<thead>
<tr>
<th>Resources</th>
<th>Cost per Unit, Can $</th>
<th>Mean No. of Units of Resources Consumed</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Scheduled Treatment Costs</td>
<td>Standard Heparin</td>
</tr>
<tr>
<td>Warfarin sodium, mg</td>
<td>0.13</td>
<td>49</td>
</tr>
<tr>
<td>Standard heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500-ml mini-bags</td>
<td>2.33</td>
<td>6.7</td>
</tr>
<tr>
<td>5000 U boluses</td>
<td>0.58</td>
<td>2.9</td>
</tr>
<tr>
<td>LMWH</td>
<td>0.20</td>
<td>0</td>
</tr>
<tr>
<td>No. of hospital days</td>
<td>487</td>
<td>6.7</td>
</tr>
<tr>
<td>Clinic visits, No.</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Routine monitoring tests</td>
<td>40-10</td>
<td>20.3</td>
</tr>
<tr>
<td>Nurse home visits</td>
<td>37</td>
<td>0</td>
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<table>
<thead>
<tr>
<th>Nonscheduled Investigation and Treatment Costs</th>
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<tbody>
<tr>
<td>Hospital admissions</td>
<td>17</td>
</tr>
<tr>
<td>Days in intensive care unit</td>
<td>1679</td>
</tr>
<tr>
<td>Days on ward</td>
<td>487</td>
</tr>
<tr>
<td>Outpatient visits†</td>
<td>25-62</td>
</tr>
<tr>
<td>Diagnostic investigations</td>
<td>37-466</td>
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<table>
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<th>Patient Costs and Lost Productivity</th>
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<tr>
<td>Patient off work, d</td>
<td>126</td>
</tr>
<tr>
<td>Caregiver off work, d</td>
<td>126</td>
</tr>
<tr>
<td>Patient travel, km</td>
<td>0.35</td>
</tr>
</tbody>
</table>

*LMWH indicates low-molecular-weight heparin; ellipses not applicable.
†Includes visits to the emergency department, family physician, or thrombosis clinic.

MEAN COSTS BY TREATMENT GROUP

Mean costs per patient by treatment group are given in
Table 3. These data indicate that there is a cost saving
in scheduled treatment costs associated with low-
molecular-weight heparin of Can $2617 per patient (95%
CI, Can $2311-$2964; P < .001). Most of this cost differ-
ence arises from differences between the 2 groups in the
use of hospital days, as indicated in Table 2. With re-
spect to nonscheduled investigations and treatment costs,
there is a nonsignificant trend toward a higher cost of
Can $85 per patient receiving low-molecular-weight hep-
arin (P = .62). Patient costs and lost productivity are sig-
nificantly lower for the low-molecular-weight heparin
group by Can $513 per patient (P = .02). Overall, the to-
Cost per patient randomized to standard heparin was Can $5323 vs Can $2278 for the low-molecular-weight heparin: a societal cost saving per patient using low-molecular-weight heparin of Can $3045 (95% CI, Can $2012-$4050; P, .001).

SENSITIVITY ANALYSIS

Alternative unit price assumptions such as a lower ward cost per day of Can $329 for a community hospital and Ontario minimum wage rate (Can $6.85 per day) for productivity losses did not significantly alter the base result. To test the generalizability of our findings to a US setting, we conducted a 2-way sensitivity analysis (Figure), varying both the hospital ward cost per day and using the US cost of enoxaparin (US $0.38/mg), in addition to displaying the 95% CIs due to sampling variation. As the figure illustrates, using a recently published US ward cost per day of US $475 (Can $665) and the US price for enoxaparin, the cost saving from treatment with low-molecular-weight heparin is predicted to be even greater in the United States than in Canada at Can $3849 (US $2750) per patient.

HEALTH-RELATED QUALITY OF LIFE

Data on health-related quality of life using the Short-Form 36 are given in Table 4. Baseline scores on all domains for both treatment groups are lower (worse) than age-matched normative scores from a healthy population. However, the change in scores from baseline to day 7 was not significantly different between the treatment groups for 7 of the 8 domains (Table 4). The one exception is the domain of social functioning, where a greater improvement was observed for the low-molecular-weight heparin group than the standard heparin group (P = .005).
shown that health-related quality of life associated with outpatient treatment is at least as good—and maybe better in some domains such as social functioning—than hospital-based heparin treatment. In the trial there was no difference in efficacy and safety between treatment groups. In summary, the economic evidence in favor of outpatient treatment with low-molecular-weight heparin is strong; in the terminology of economic evaluation, it exhibits dominance or a "win-win" situation of reduced cost with no compromise in clinical outcomes or patient quality of life.

To our knowledge, this is the first economic evaluation of outpatient treatment with low-molecular-weight heparin where data on costs, clinical outcomes, and health-related quality of life were collected prospectively as part of a randomized trial. A previous economic analysis by Hull et al19 based on their trial of in-hospital use of standard heparin vs low-molecular-weight heparin predicted cost savings with home-based low-molecular-weight heparin treatment by assuming that 37% of patients receiving low-molecular-weight heparin could have been sent home for treatment. But in the absence of observation and data on the costs and consequences of actually sending patients home for treatment, the accuracy of such predictions is difficult to verify. A Swedish study20 has also estimated cost savings associated with low-molecular-weight heparin outpatient treatment, but this was a nonrandomized study.

In addition to conventional quantification of uncertainty from sampling variation using 95% CIs, we undertook a number of sensitivity analyses to assess the impact on results of alternative assumptions regarding, for example, prices for resources. These analyses indicated that the result of cost savings is robust within a wide range of alternative assumptions about prices. Such analyses are also helpful in examining the geographic generalizability of our results to non-Canadian settings. Specifically, we quantified the relationship between the hospital cost per day, the cost of enoxaparin, and the predicted savings per patient; this permits readers with higher or lower daily costs than Canadian hospitals to quantify likely cost savings in their settings. The purpose of this sensitivity analysis was to examine whether the main result was robust if US prices were used for the 2 key cost drivers, ie, the price of enoxaparin and the cost of a hospital day. This sensitivity analysis suggests that, even though the cost of enoxaparin is higher in the United States than in Canada, the avoidance of more costly hospital days will likely result in greater overall savings in the United States.

The Short-Form 36 is a well-validated and widely used generic measure of health-related quality of life. At day 7 after randomization, our results indicated no statistically significant difference in change over baseline scores between treatment groups for 7 of the 8 domains (Table 4). The one exception was social functioning, which was significantly worse in the hospital-based standard heparin group (P = .005). This result is consistent with a European trial of in-hospital standard heparin vs home-based low-molecular-weight heparin (the Tassman Study) where social functioning and physical functioning were found to be better in the outpatient group using a shorter, 20-item version of the Short-Form 36. The reproducibility of this result is encouraging and indicates that, at minimum, the health-related quality of life of home-treated patients was no worse than their counterparts treated in the hospital, and is likely to be equivalent or better.

The results of our economic evaluation of the randomized trial are generalizable to clinical practice. The feasibility of out-of-hospital administration of low-molecular-weight heparin outside of a trial setting has recently been reported in 2 prospective cohort studies. The protocol for the randomized trial did not require extra tests and procedures, which could have impacted on the economic evaluation; hence the study replicated how patients are managed in routine practice.

Restricting the focus of our economic analysis to the stratum of patients who presented with proximal vein thrombosis as outpatients does not introduce bias into the treatment comparisons for clinical events, costs, or quality of life because randomization was stratified by the 3 groups of patient presentation: (1) outpatients; (2) those admitted at night or during the weekend who, for logistic reasons, could not be enrolled in the study immediately; and (3) patients who were already in the hospital. We chose to study the outpatient stratum because the cost-effectiveness of a drug is conditional on how it is used in the clinical management of a well-defined group of patients. Our study provides the economic evidence that a clinical strategy of attempting home-based treat-

*LMWH indicates low-molecular-weight heparin. Each domain score can range from 0 to 100 with higher scores denoting better functioning.
ment with low-molecular-weight heparin for persons presenting with proximal vein thrombosis at outpatients is an efficient use of resources. It should also be noted that our cost analysis embodies uncertainty about the feasibility of initial home-based treatment by following the principle of intention-to-treat, such that the costs of the 29 patients (of 149) assigned to low-molecular-weight heparin who were initially hospitalized, primarily to learn how to self-inject the drug, are included in the mean cost per patient for the group.

Economic appraisal is becoming a routine and accepted part of evaluating new pharmaceuticals and clinical procedures. In both a tax-financed health care system such as in Canada and a predominantly insurance-financed system such as in the United States, health care reimbursement decision makers are seeking new ways to reduce costs while maintaining quality of care. The economic attractiveness of home-based treatment with low-molecular-weight heparin has already led to its adoption by Kaiser Permanente, a large health maintenance organization in southern California, and details of their pharmacy-managed program have been published. We would like to acknowledge the contributions of the following study investigators at the participating clinical centers: Jack Hirsh, MD, Jeffrey Weitz, MD, Jeffrey Ginsberg, MD, and Alexander G. Turpie, MD, Hamilton Health Sciences Corporation, Hamilton, Ontario; Peter Powers, MD, St. Joseph’s Hospital, Hamilton; Jacques Leclerc, MD, Montreal General Hospital, Montreal, Quebec; David Anderson, MD, Victoria General Hospital, Halifax, Nova Scotia; Christine Demers, MD, St. Sacrement Hospital, Quebec City, Quebec; Louis Desjardins, MD, Centre Hospitalier de l’Universite Laval, Quebec City; Jean Cusson, MD, Hotel-Dieu de Montreal, Montreal; Jeannine Kassis, MD, Maisonneuve-Rosemont Hospital, Montreal; William Geerts, MD, Sunnybrook Health Science Centre, Toronto, Ontario; Michael Kovacs, MD, Victoria Hospital, London, Ontario; Motra Cruickshank, MD, University Hospital, London.

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Accepted for publication February 15, 1999.

Funded in part by a grant from Rhone-Poulenc Rorer, Montreal, Quebec (Dr O’Brien). Dr O’Brien is also supported by a career award in health sciences from the Medical Research Council of Canada and the Prescription Drug Manufacturers’ Association of Canada, Ottawa, Ontario.

We would like to acknowledge the contributions of the following study investigators at the participating clinical centers: Jack Hirsh, MD, Jeffrey Weitz, MD, Jeffrey Ginsberg, MD, and Alexander G. Turpie, MD, Hamilton Health Sciences Corporation, Hamilton, Ontario; Peter Powers, MD, St. Joseph’s Hospital, Hamilton; Jacques Leclerc, MD, Montreal General Hospital, Montreal, Quebec; David Anderson, MD, Victoria General Hospital, Halifax, Nova Scotia; Christine Demers, MD, St. Sacrement Hospital, Quebec City, Quebec; Louis Desjardins, MD, Centre Hospitalier de l’Universite Laval, Quebec City; Jean Cusson, MD, Hotel-Dieu de Montreal, Montreal; Jeannine Kassis, MD, Maisonneuve-Rosemont Hospital, Montreal; William Geerts, MD, Sunnybrook Health Science Centre, Toronto, Ontario; Michael Kovacs, MD, Victoria Hospital, London, Ontario; Motra Cruickshank, MD, University Hospital, London.

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