Economic Analysis of Low-Dose Heparin vs the Low-Molecular-Weight Heparin Enoxaparin for Prevention of Venous Thromboembolism After Colorectal Surgery

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**Background:** Low-dose heparin and low-molecular-weight heparin are effective strategies for preventing venous thromboembolism in colorectal surgery. The economic attractiveness of these 2 strategies in North America is unknown. We conducted an economic analysis of low-dose heparin calcium compared with enoxaparin sodium, a low-molecular-weight heparin, for thromboembolism prophylaxis after colorectal surgery.

**Methods:** We used decision analysis, with an economic perspective of a third-party payer. Efficacy data were obtained from the Canadian Multicentre Colorectal Deep Vein Thrombosis Prophylaxis Trial and a literature review. Canadian costs for diagnosis and treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and major bleeding were obtained from chart review and a national hospital database of colorectal surgery; American costs were obtained from published literature. The main outcomes were incremental benefits (symptomatic DVTs, symptomatic PEs, and major bleeding events avoided) and incremental costs for every 1000 patients treated.

**Results:** In the Canadian Colorectal Trial, the relative risk of DVT and PE for enoxaparin compared with low-dose heparin was 1.0 (95% confidence interval, 0.7-1.5), and the relative risk of major bleeding was 1.8 (95% confidence interval, 0.8-3.9). With the use of these data in the baseline analysis, a strategy of enoxaparin prophylaxis was associated with equal numbers of symptomatic DVTs and PEs, and an excess of 12 major bleeding episodes for every 1000 patients treated, with an additional cost of $86,050 (Canadian data) or $145,667 (US data). In a sensitivity analysis using optimal assumptions for efficacy and safety of enoxaparin (relative risk of DVT, 0.8; relative risk of PE, 0.4; relative risk of major bleeding, 1.0), a strategy of enoxaparin prophylaxis was associated with 0.8 fewer symptomatic DVT, 3 fewer symptomatic PEs, and equal numbers of major bleeding episodes for every 1000 patients treated, with an additional cost of $15,217 (Canadian data) or $107,614 (US data).

**Conclusion:** Although heparin and enoxaparin are equally effective, low-dose heparin is a more economically attractive choice for thromboembolism prophylaxis after colorectal surgery.

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Colorectal surgery is associated with a high risk of venous thromboembolism, including deep vein thrombosis (DVT) and pulmonary embolism (PE).\(^1\) Low-dose heparin is the most widely accepted method of preventing venous thromboembolism in general surgery because it is effective, safe, feasible, and economically attractive, compared with no prophylaxis.\(^2\) However, approximately 10% to 15% of patients who undergo colorectal surgery will develop venous thromboembolism despite the use of low-dose heparin prophylaxis.\(^3\) Approximately 120,000 patients had colorectal surgery for colorectal cancer in 1990 in North America,\(^4\) and many others had surgery for inflammatory bowel disease and other conditions, so identifying the most effective and economically attractive method of thromboembolism prophylaxis is an important goal.

Low-molecular-weight heparins (LMWHs) are a potentially advantageous new option for prevention of venous thromboembolism after colorectal surgery. The LMWHs are effective for preventing DVT in other moderate- and high-risk surgical populations, and they appear safe with regard to major bleeding.\(^5,6\)\(^6\) The LMWHs may be conveniently given by once-daily injection. However, the cost of LMWHs in North America is at least 10 times the cost of low-dose heparin.

In North America, the economic attractiveness of LMWH compared with that of low-dose heparin in colorectal surgery remains uncertain. Two previous eco-
METHODS

FUNDING

Unrestricted funding for this analysis was provided in part by Rhône-Poulenc Rorer (Quebec, Quebec), the manufacturer of enoxaparin. The terms of the contract with Rhône-Poulenc Rorer were determined at the outset after we proposed the study design and methods, including measurement, modeling, and analytical strategies. We retained the rights to control entirely the methods and conclusions throughout the study and to publish or otherwise disseminate the results of the study and their conclusions regardless of the outcome. Rhône-Poulenc Rorer received a copy of the report and manuscript before publication but was specifically precluded from influencing us at any stage after the contract was signed.

COMPARATIVE STRATEGIES

Two management strategies were compared in the decision analytical model. The first strategy was a policy of routine prophylaxis with low-dose heparin sodium (5000 U) injected subcutaneously 3 times per day beginning 2 hours before surgery. The second strategy was a policy of routine prophylaxis with enoxaparin sodium, 40 mg injected subcutaneously once daily, beginning 2 hours before surgery. We assumed that prophylaxis was given for 7 days (ie, 21 doses of low-dose heparin or 7 doses of enoxaparin), based on the median duration of prophylaxis from the Canadian Multicenter Trial. We also assumed that there was no routine laboratory monitoring for either strategy because the partial thromboplastin time does not change with low-dose heparin or LMWH, and heparin-induced thrombocytopenia is rare during the first 7 days of prophylaxis.14

DECISION TREE

We constructed a decision analytic tree by means of SMLTREE software (version 2.9; SMLTREE Vebio; Jim Hollenberg, New York, NY). A simplified version of the tree is shown in the Figure. We assumed that patients were not screened for asymptomatic DVT.13 We also assumed that any patient who developed symptoms suggestive of postoperative DVT would undergo compression ultrasound examination of the leg (thigh and calf). If the result were positive, then the patient would be treated (“detected” in the Figure). If the result were negative, the patient would have a second ultrasound at 5 to 7 days.16 If the second ultrasound were positive, the patient would be treated (“detected”). If the second ultrasound were negative, no further testing would be done (“not detected”). We assumed that treatment of detected symptomatic proximal or distal DVT, or PE, would be intravenous standard heparin, followed by outpatient warfarin sodium therapy for 3 months.17-19 The risk of major bleeding during treatment was considered elevated because of the recent surgery.20 If a patient developed major bleeding during treatment, anticoagulation would be discontinued and an inferior vena cava filter would be inserted.

OUTCOMES

The decision analytic model focused on clinically relevant outcomes, including symptomatic DVT, symptomatic PE, and major bleeding. In the Canadian Trial, major bleeding was defined as clinically overt bleeding associated with a decrease in hemoglobin level of at least 20 g/L, or requiring transfusion of at least 2 units of red blood cells, or reoperation.12 We did not include minor bleeding complications, since the economic consequences of such complications are small.9

We did not explicitly model outcomes related to postphlebitic syndrome. We recognized that symptomatic DVT may be associated with long-term costs related to postphlebitic syndrome,21 so we used a wide range of costs for symptomatic DVT in our sensitivity analyses. Asymptomatic DVT may not be associated with an increased risk of postphlebitic syndrome,22,23 so we did not model any economic consequences of asymptomatic DVT in the baseline analysis, but we did include a range of costs in the sensitivity analyses. We also assumed that patients with treated nonfatal PE suffered no long-term cardiorespiratory consequences.

PROBABILITY VALUES

In the baseline analysis, we used estimates of efficacy obtained from the Canadian Multicenter Trial.12 We also conducted a MEDLINE search for the years 1966 through 1997 and found several other trials that compared low-dose heparin and enoxaparin in colorectal or general surgery.13,24-27 As well as trials and meta-analyses of other LMWHs in abdominal surgery.9,28,29 These studies were used to establish reasonable ranges of values for the sensitivity analyses. Other relevant probability values were obtained from the published literature.20,30-36

ECONOMIC ASSUMPTIONS AND PERSPECTIVE

The primary economic perspective was that of a third-party payer; the direct cost of providing health care was the primary consideration. We also estimated the indirect costs of complications related to loss of productive time incurred by prolonged hospitalization, convalescence, nomic analyses of LMWH and low-dose heparin in abdominal surgery, from New Zealand and Sweden, concluded that LMWH is economically attractive.9,10 Both analyses were limited by a low cost of administering LMWH prophylaxis relative to the cost in North America (1.3-1.4 times the cost of low-dose heparin) and failure to perform sensitivity analyses on the choice between LMWH and low-dose heparin.

One published North American economic analysis compared low-dose heparin with the LMWH dalteparin sodium in moderate-risk abdominal surgery patients and concluded that low-dose heparin was the more economical choice.11 Since this analysis was published, 2 large randomized trials of thromboembolism prophylaxis in high-risk abdominal surgery patients have been reported; both studies used venographic outcomes and a different LMWH, enoxaparin sodium.12,13

The purpose of this study was to evaluate the economic attractiveness of the LMWH enoxaparin with low-dose heparin calcium for the prevention of thromboembolism after colorectal surgery, using current efficacy data and North American cost data. The analysis was con-
physician visits, and premature death by means of the 1993 industrial aggregate of average yearly earnings ($24,698) in Canada. Individuals were assumed to be potentially productive until age 65 years. The mean age for patients undergoing colorectal surgery was assumed to be 51 years, based on the mean age of patients in the Canadian Multi-center Trial. The long-term indirect costs were discounted at a rate of 5% per year. This discount rate was varied in the sensitivity analyses from 2% to 8%.

COSTS OF PROPHYLAXIS

For the Canadian analysis, we obtained 1995 inpatient costs for administering low-dose heparin and enoxaparin from the Sunnybrook Health Science Centre (Toronto, Ontario). In our baseline analysis, we did not include nursing time in the cost of prophylaxis, because cost savings are not realized unless nursing staff can be reduced, or unless saved nursing time can be reallocated to activities that reduce the overall cost of care. In our sensitivity analyses, we did consider the costs of saved nursing time. We obtained estimates of nursing time for subcutaneous injection of prefilled syringes, including disposal and documentation, from the Toronto Hospital Nursing Workload Measurement Project.

For the US analysis, we obtained costs of prophylaxis from published economic analyses and from Rhône-Poulenc Rorer.

COSTS OF SHORT-TERM OUTCOMES RELATED TO THROMBOEMBOLISM AND MAJOR BLEEDING

We obtained unit costs for bed-days, laboratory testing, blood bank, radiology, operating rooms, and other hospital services from the Sunnybrook Health Science Centre Decision Support Department for the 1994 fiscal year. These unit costs reflect the actual fixed and variable costs of providing each service to an individual hospitalized patient. We obtained physician costs from the 1993 Ontario Health Insurance Plan schedule of payments. The 1995 drug costs for treating established DVT and PE with intravenous heparin and oral warfarin were obtained from the Sunnybrook Health Science Centre pharmacy, and laboratory costs from the Sunnybrook Health Sciences Centre Decision Support Department. For indirect (societal) costs, loss of productive time related to physician visits and laboratory tests was estimated.

In our sensitivity analyses, we also included the range of costs for DVT, PE, and major bleeding that have been previously reported. For the US analysis, we obtained costs for DVT, PE, and major bleeding from published analyses in general abdominal surgery and other settings.

ANALYTICAL METHOD

We calculated the costs and number of events (symptomatic DVT, PEs, and major bleeding episodes) for every 1000 persons treated with either low-dose heparin or enoxaparin, then calculated the difference between the 2 strategies. All Canadian costs are reported in Canadian dollars, while all US costs are reported in US dollars. One-, 2-, and 3-way sensitivity analyses were performed on all variables within a clinically relevant range. Any combinations of variables that affected the conclusions of our analysis were explored and are reported.

Second, we reviewed charts of inpatients who were not part of the clinical trial and measured the volume of services for typical cases of symptomatic DVT (n = 28), PE (n = 55), and major postoperative bleeding (n = 16). Not all of the cases of DVT and PE were postoperative.

Third, we obtained data from the Canadian Institute for Health Information, a national database, for all patients in Canada who underwent colorectal surgery procedures (N = 17,459) during the 1993-1994 fiscal year. The presence of a DVT, PE, or bleeding complication was based on discharge coding, with the use of International Classification of Diseases, Ninth Revision, codes 451.1, 415.1, 997.2, and 998.1. There were 193 thromboembolic (DVT and PE) complications and 435 bleeding complications. We wanted to ensure that any additional length of stay resulted from the complication rather than comorbidity associated with the complication. Therefore, we created 16 patient strata based on 4 binary variables (age >70 years, rectal or colon surgery, presence of malignant neoplasm, and urgency of surgery). For each stratum, we compared the length of stay for patients who did and did not develop thromboembolism or major bleeding. We used the incremental length of stay associated with thromboembolism and major bleeding as an estimate of the incremental volume of services required to treat the complication.

Outpatient costs for treating DVT and PE were estimated by means of physician costs from the 1995 Ontario Health Insurance Plan schedule of benefits, drug costs from the Sunnybrook Health Science Centre pharmacy, and laboratory costs from the Sunnybrook Health Sciences Centre Decision Support Department. For indirect (societal) costs, loss of productive time related to physician visits and laboratory tests was estimated.

In our sensitivity analyses, we also included the range of costs for DVT, PE, and major bleeding that have been previously reported.

For the US analysis, we obtained costs for DVT, PE, and major bleeding from published analyses in general abdominal surgery and other settings.

RESULTS

EFFICACY AND SAFETY OF LOW-DOSE HEPARIN AND ENOXAPARIN

In the Canadian Colorectal DVT Prophylaxis Trial, low-dose heparin and enoxaparin were equally efficacious for preventing DVT (relative risk, 1.0; 95% confidence interval, 0.67-1.5). We identified 6 other studies comparing low-dose heparin and enoxaparin in general surgery (Table 1). All were randomized trials with at least 90% patient follow-up and intention-to-treat analyses, and all but 2 were double-blinded. In these studies, the relative risk of DVT with enoxaparin ranged from 0.5 to 1.3. In the Canadian Colorectal Trial, the relative risk of major bleeding associated with enoxaparin was 1.8 (95% confidence interval, 0.8-3.9), while in the other studies, the relative risk for major bleeding ranged from 0.6 to 1.4.
Only 1 symptomatic confirmed PE occurred in the Canadian trial. Therefore, in the baseline analysis we assumed that the relative risk of symptomatic PE was the same as the relative risk of DVT. For all trials comparing low-dose heparin and enoxaparin in abdominal surgery, the rate of symptomatic PE was 0.3% (8/2763) for low-dose heparin and 0.1% (3/2779) for enoxaparin (relative risk, 0.37; 95% confidence interval, 0.1-1.4), including 3 confirmed fatal PEs (2 with low-dose heparin and 1 with enoxaparin). Therefore, we used a value of 0.4 for the relative risk of PE with enoxaparin in some of our sensitivity analysis.

COSTS

With the use of Canadian data, the cost of 7 days of prophylaxis was $15.96 for low-dose heparin and $56.07 for enoxaparin; the corresponding US costs were $36.54 and $158.20 (Table 2).

The costs for symptomatic detected DVT, symptomatic PE, and major bleeding are summarized in Table 3. Based on chart review of patients enrolled in the Canadian Colorectal DVT Trial, the cost of diagnosis and treatment of DVT was $0, because all of these patients had asymptomatic DVT detected by venography,

Table 1. Randomized Trials Comparing LD Heparin and Enoxaparin in Abdominal Surgery*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>DVT, No./Total No. (%)</th>
<th>RR of DVT</th>
<th>Major Bleeding, No./Total No. (%)</th>
<th>RR of Major Bleeding</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium</td>
<td>LD Heparin Calcium</td>
<td>Enoxaparin LD Heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McLeod et al,12 1997</td>
<td>44/468 (9.4)</td>
<td>44/468 (9.4)</td>
<td>1.0 (0.7-1.5)</td>
<td>18/674 (2.7)</td>
<td>10/675 (1.5)</td>
</tr>
<tr>
<td>ENOXACAN,13 1997</td>
<td>46/312 (14.7)</td>
<td>58/319 (18.2)</td>
<td>0.8 (0.6-1.2)</td>
<td>16/560 (2.9)</td>
<td>23/555 (4.1)</td>
</tr>
<tr>
<td>Samama et al,27 1988</td>
<td>3/106 (2.8)</td>
<td>3/110 (2.7)</td>
<td>1.0 (0.2-5.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Studies With Enoxaparin Sodium, 20 mg/d

<table>
<thead>
<tr>
<th>Source, y</th>
<th>DVT, No./Total No. (%)</th>
<th>RR of DVT</th>
<th>Major Bleeding, No./Total No. (%)</th>
<th>RR of Major Bleeding</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Enoxaparin Sodium</td>
<td>LD Heparin Calcium</td>
<td>Enoxaparin LD Heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurmohamed et al,24 1992</td>
<td>58/718 (8.1)</td>
<td>45/709 (6.3)</td>
<td>1.3 (0.9-1.9)</td>
<td>11/718 (1.5)</td>
<td>18/709 (2.5)</td>
</tr>
<tr>
<td>Gazzaniga et al,25 1993</td>
<td>3/561 (0.5)</td>
<td>6/561 (1.1)</td>
<td>0.5 (0.1-2.0)</td>
<td>29/561 (5.2)</td>
<td>34/561 (6.1)</td>
</tr>
<tr>
<td>Samama et al,27 1988</td>
<td>6/159 (3.8)</td>
<td>12/158 (7.6)</td>
<td>0.5 (0.2-1.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*LD indicates low-dose; DVT, deep vein thrombosis; RR, relative risk; CI, confidence interval; and NA, not applicable. All studies used LD heparin calcium, 5000 U every 8 hours, unless otherwise noted.
which was not associated with additional inpatient costs. Based on chart review of patients not enrolled in the clinical trial, the cost of diagnosis and treatment of symptomatic DVT was $5800 (including $2710 for increased length of stay), while the cost of symptomatic PE was $6200 (including $3320 for increased length of stay). Based on the Canadian national hospital database, the cost of increased length of stay because of thromboembolism complications was $3410.

Based on chart review of patients enrolled in the Canadian Colorectal Trial, the cost of a major bleeding episode was $3830 (including $3100 for increased length of stay). Based on chart review of patients not enrolled in the Canadian Colorectal Trial, the cost of a major bleeding episode was $2820 (including $2080 for increased length of stay). Based on the Canadian national hospital database, the cost of increased length of stay because of a major bleeding episode was $1820.

**BASELINE ANALYSIS**

The baseline probabilities used in the decision tree are listed in Table 4. In the baseline analysis, we used the efficacy data from the Canadian Multicenter Trial. Enoxaparin prophylaxis was associated with equal numbers of symptomatic DVT and PEs, 12 additional cases of major bleeding, and an additional cost of $86 050 (Canadian data) and $145 667 (US data) for every 1000 patients treated (Table 5). If the cost of nursing time is included, the total cost for 7 days of prophylaxis was $1820.

**Table 2. Costs of Prophylaxis With Low-Dose Heparin and Enoxaparin**

| Drug cost per day | 0.57 | 8.00 |
| Syringe and accessories per day | 0.72 | Prefilled |
| Alcohol swabs per day | 0.03 | 0.01 |
| Pharmacy labor per day | 0.96 | 0 |
| Total Daily Cost | 2.28 | 8.01 |

**Table 3. Costs for Short-term Outcomes Related to Thromboembolism and Bleeding**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Direct*</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetected symptomatic DVT‡</td>
<td>0 (0-11 000)</td>
<td>0 (0-5000)</td>
</tr>
<tr>
<td>Detected symptomatic DVT</td>
<td>5800 (1000-11 000)</td>
<td>1315 (1000-5000)</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>6200 (2400-19 000)</td>
<td>1315 (1000-5000)</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>6200 (2400-19 000)</td>
<td>250 000 (20 000-500 000)</td>
</tr>
<tr>
<td>Nonfatal major bleeding</td>
<td>3830 (1200-5400)</td>
<td>880 (400-2000)</td>
</tr>
<tr>
<td>Total Cost for 7 days of Prophylaxis Including Nursing Time</td>
<td>60.27</td>
<td>78.54</td>
</tr>
</tbody>
</table>

*References 6 and 38 to 41.
†References 11, 38, 41, 43, and 45.
‡DVT indicates deep vein thrombosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Value</th>
<th>Range for Sensitivity Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of DVT, %</td>
<td>9.4</td>
<td>1-20</td>
</tr>
<tr>
<td>Proximal</td>
<td>2.7</td>
<td>0.3-5</td>
</tr>
<tr>
<td>Distal</td>
<td>6.7</td>
<td>0.7-15</td>
</tr>
<tr>
<td>Proportion of DVTs that are symptomatic, %</td>
<td>5</td>
<td>0-50</td>
</tr>
<tr>
<td>Compression ultrasound for symptomatic legs, %</td>
<td>95</td>
<td>60-100</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>95</td>
<td>60-100</td>
</tr>
<tr>
<td>Specificity</td>
<td>80</td>
<td>0-100</td>
</tr>
<tr>
<td>Probability of conversion from negative to positive ultrasound, %</td>
<td>3</td>
<td>0-10</td>
</tr>
<tr>
<td>PE while receiving low-dose heparin calcium, %</td>
<td>0.5</td>
<td>0.1-0.7</td>
</tr>
<tr>
<td>Proportion of PEs that are fatal, %</td>
<td>22</td>
<td>0-50</td>
</tr>
<tr>
<td>Major bleeding while receiving low-dose heparin, %</td>
<td>1.5</td>
<td>0.1-10</td>
</tr>
<tr>
<td>Proportion of major bleeding episodes that are fatal, %</td>
<td>0.1</td>
<td>0-0.2</td>
</tr>
<tr>
<td>Relative risk of major bleeding during treatment for DVT/PE</td>
<td>2.0</td>
<td>1-10</td>
</tr>
</tbody>
</table>

*DVT indicates deep vein thrombosis; PE, pulmonary embolism.
cluded in the cost of prophylaxis, then the enoxaparin strategy was associated with an additional cost of $56,510 (Canadian data) or $117,667 (US data).

SENSITIVITY ANALYSES

The model was most sensitive to variations in the drug cost of enoxaparin, the relative risk of DVT and PE, and the relative risk of major bleeding. Therefore, we defined several clinically relevant scenarios to explore the effect of these variables on our analysis (Table 6). The first scenario assumed that enoxaparin sodium prophylaxis is given at 20 mg (2000 anti-Xa units [2000 anti-activated factor 10 units]) daily, a 50% cost reduction compared with the 40-mg dose. The 20-mg dose may be associated with more DVT, but there may be less major bleeding than with low-dose heparin. In this scenario, the enoxaparin strategy was associated with 0.8 fewer symptomatic DVTs, 1.5 more symptomatic PEs, 6 fewer episodes of major bleeding, and an additional cost of $6746 (Canadian data) or $40,406 (US data) for every 1000 patients treated.

We then explored a scenario in which enoxaparin was more effective than low-dose heparin for preventing DVT (relative risk, 0.8) and PE (relative risk, 0.4) without excess bleeding (relative risk, 1.0). In this optimal efficacy scenario, the enoxaparin strategy was associated with 0.8 fewer symptomatic DVT, 3 fewer symptomatic PEs, no excess major bleeding, and an additional cost of $15,217 (Canadian data) or $107,614 (US data) for every 1000 patients treated.

Finally, we explored a scenario in which enoxaparin was as effective as low-dose heparin for preventing DVT and PE (relative risk, 1.0) but caused less major bleeding (relative risk, 0.6). In this optimal safety scenario, the enoxaparin strategy was associated with equal numbers of symptomatic cases of DVT and PE, 6 fewer episodes of major bleeding, and an additional cost of $17,140 (Canadian data) or $109,656 (US data) for every 1000 patients treated.

The model was not sensitive to 2- or 3-way variations in other variables except the relative risk of PE and the inclusion of indirect (societal) costs of fatal PE. If either strategy was associated with a lower risk of PE, including fatal PE, then the high indirect cost of fatal PE made that strategy economically attractive. For example, if the relative risk of PE (including fatal PE) with enoxaparin was 0.7, then an enoxaparin strategy was associated with 1.2 fewer nonfatal PEs, 0.3 fewer fatal PEs, and an indirect (societal) cost savings of $6000 (Canadian data) for every 1000 patients treated.

Our analysis indicates that low-dose heparin is the economically attractive choice for the prevention of DVT after colorectal surgery. Low-dose heparin was equally effective, safer, and less expensive in the baseline analysis and was therefore the dominant choice. Low-dose heparin remained attractive even when optimal assumptions regarding efficacy and safety of enoxaparin were made.

Our analysis has several strengths. First, we used efficacy and safety estimates from a large randomized double-blind trial, as well as other published randomized trials comparing low-dose heparin with enoxaparin in other general surgical populations. Second, our Canadian cost estimates were derived from distinct complementary sources, including direct review of patient charts at multiple hospitals, as well as a national database of more than 17,000 patients undergoing colorectal surgery. Third, we focused on clinically relevant outcomes, including symptomatic DVT, symptomatic PE, and major bleeding. Finally, we ensured our freedom to conduct and report this analysis without constraint from the pharmaceutical manufacturer.

Table 5. Results of Baseline Analysis for Every 1000 Patients Treated*

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin sodium</td>
<td>4</td>
<td>5</td>
<td>27</td>
<td>218,307</td>
<td>242,778</td>
</tr>
<tr>
<td>LD heparin</td>
<td>4</td>
<td>5</td>
<td>15</td>
<td>132,257</td>
<td>97,111</td>
</tr>
<tr>
<td>Difference</td>
<td>0 Prevented</td>
<td>0 Prevented</td>
<td>12 Caused</td>
<td>+86,050</td>
<td>+145,667</td>
</tr>
</tbody>
</table>

* DVT indicates deep vein thrombosis; PE, pulmonary embolism; and LD, low-dose.

Table 6. Results of Sensitivity Analyses*

<table>
<thead>
<tr>
<th>RR</th>
<th>DVT Prevented/ Caused, No.</th>
<th>PE Prevented/ Caused, No.</th>
<th>Major Bleeding Prevented/ Caused, No.</th>
<th>Additional Cost of Enoxaparin Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline analysis</td>
<td>1.0</td>
<td>1.0</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>Enoxaparin sodium, 20 mg/d</td>
<td>1.3</td>
<td>1.3</td>
<td>0.6</td>
<td>1.2 Caused</td>
</tr>
<tr>
<td>Optimal efficacy</td>
<td>0.8</td>
<td>0.4</td>
<td>1.0</td>
<td>0.8 Prevented</td>
</tr>
<tr>
<td>Optimal safety</td>
<td>1.0</td>
<td>1.0</td>
<td>0.6</td>
<td>0</td>
</tr>
</tbody>
</table>

* For each sensitivity analysis, we calculated the incremental outcomes (outcomes with enoxaparin strategy – outcomes with low-dose heparin calcium strategy) and the additional cost (costs with enoxaparin strategy – costs with low-dose heparin strategy) for every 1000 patients treated. RR indicates relative risk of outcome with enoxaparin compared with low-dose heparin, DVT, deep vein thrombosis, and PE, pulmonary embolism.
There are some potential limitations to our analysis. The Canadian Multicentre Trial, as well as the ENOXACAN study, used enoxaparin sodium, 40 mg daily (4000 anti-Xa units) and observed relatively more bleeding with enoxaparin than with low-dose heparin (relative risks, 1.8 and 1.4, respectively). It is possible that a lower dose of enoxaparin may be safer with regard to major bleeding, but equally effective at preventing thromboembolism. However, our sensitivity analyses indicate that even if enoxaparin prophylaxis were not associated with excess major bleeding, it would remain economically unattractive.

A second limitation of our baseline analysis is the assumption that enoxaparin does not reduce the risk of PE or fatal PE compared with low-dose heparin. There are insufficient data from randomized trials to make firm conclusions regarding the effect of enoxaparin on PE. We addressed this limitation in our sensitivity analyses by making favorable assumptions regarding the risk of PE with enoxaparin, and our conclusions were not changed. Our conclusions were affected only if we assumed that enoxaparin reduces fatal PEs and considered the indirect (societal) costs of fatal PE. However, only 3 confirmed fatal PEs have been reported among approximately 5500 general surgical patients randomized to low-dose heparin or enoxaparin. We believe that the choice between low-dose heparin and enoxaparin should not be based on a potential reduction in fatal PE by enoxaparin.

A final limitation relates to our cost estimates for DVT, PE, and major bleeding. Our Canadian unit costs were derived from a single hospital and may not represent costs at other Canadian hospitals. Our US costs were obtained from published studies from a few hospitals, and some of these studies did not clearly distinguish between costs and charges. We addressed the uncertainty regarding the cost estimates by conducting extensive sensitivity analyses, and we found that our conclusions were not sensitive to wide variations in these cost estimates.

Our analysis suggests that enoxaparin has little role in the prevention of DVT in high-risk abdominal surgery. The convenience of once-daily injection does not justify the substantial additional costs. It is unlikely that enoxaparin will be economically attractive in other abdominal surgery, where the frequency of DVT is lower. By contrast, enoxaparin is effective and safe for the prevention of DVT in surgical populations at highest risk for thromboembolism, such as those with major trauma, spinal cord injury, total knee replacement, and hip repair or arthroplasty, in the hip surgery population, enoxaparin is economically attractive.

We conclude that while low-dose heparin and enoxaparin are equally effective, low-dose heparin is a more economical choice than enoxaparin for thromboembolism prophylaxis after colorectal surgery.

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