Cost-effectiveness of enoxaparin versus warfarin prophylaxis against deep-vein thrombosis after total hip replacement

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Objective: To compare the efficacy and cost-effectiveness of enoxaparin, a low-molecular-weight heparin derivative, with that of low-dose warfarin in the prevention of deep-vein thrombosis (DVT) after total hip replacement.
Data sources: English-language articles on enoxaparin and warfarin prophylaxis in patients undergoing total hip replacement published from January 1982 to December 1992.
Study selection: Four trials of enoxaparin (involving 567 patients) and six trials of warfarin (involving 630) met the following criteria: randomized controlled trial, prophylaxis started no later than 24 hours after surgery and continued for at least 7 days, warfarin dose monitored and adjusted appropriately, enoxaparin dosage 30 mg twice daily, and DVT confirmed by bilateral venography.
Data extraction: Rates of DVT, cost of prophylaxis, diagnosis and treatment per patient, rate of pulmonary embolism (PE), number of deaths and incremental cost-effectiveness (cost per life-year gained).
Data synthesis: The pooled rate of DVT was 13.6% with enoxaparin (95% confidence interval [CI] 10.9% to 16.3%) and 20.6% with warfarin (95% CI 17.4% to 23.8%). At a cost of $19.55 per day for enoxaparin the total cost per patient, including prophylaxis and management of DVT, exceeded that per patient receiving warfarin by about $121. For every 10 000 patients treated the use of enoxaparin will prevent 47 cases of DVT, 3 cases of PE and 4 deaths. Thus, the estimated incremental cost-effectiveness of enoxaparin is $29 120 per life-year gained.
Conclusion: On the basis of current Canadian cost-effectiveness guidelines the results of this study would be considered moderate to strong evidence to adopt enoxaparin prophylaxis against DVT after total hip replacement. However, because of the limited data the estimates are uncertain. Future trials should compare enoxaparin and warfarin and incorporate a prospective economic appraisal.

Objectif : Comparer l'efficacité et le coefficient coût-efficacité de l'enoxaparine, dérivé de faible poids moléculaire de l'héparine, à ceux de la warfarine à faible dose dans la prévention de la thrombose veineuse profonde (TVP) après un remplacement total de la hanche.
Sources de données : Articles en anglais, publiés de janvier 1982 à décembre 1992, sur la prophylaxie à l'enoxaparine et à la warfarine chez des patients ayant subi un remplacement total de la hanche.
Sélection d'études : Quatre études cliniques sur l'enoxaparine (567 patients) et six études

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cliniques sur la warfarine (630 patients) satisfaisaient aux critères suivants : étude aléatoire contrôlée, prophylaxie amorcée au plus tard 24 heures après l'intervention chirurgicale et maintenue pendant au moins 7 jours, dose de warfarine contrôlée et rajustée en conséquence, dose d'enoxaparine de 30 mg deux fois par jour et TVP confirmée par veinographie bilatérale.

Extraction de données : Taux de TVP, coût de la prophylaxie, du diagnostic et du traitement par patient, taux d'embolie pulmonaire (EP), nombre de décès et augmentation du coefficient coût-efficacité (coût par année de vie gagnée).

Synthèse des données : Le taux regroupé de TVP s'établissait à 13,6 % dans le cas de l'enoxaparine (intervalle de confiance [IC] à 95 % de 10,9 % à 16,3 %) et à 20,6 % dans celui de la warfarine (IC à 95 % de 17,4 % à 23,8 %). Pour un coût de 19,55 $ par jour dans le cas de l'enoxaparine, le coût total par patient, y compris la prophylaxie et le traitement de la TVP, a dépassé d'environ 121 $ le coût par patient traité à la warfarine. Par tranche de 10 000 patients traités, l'utilisation de l'enoxaparine préviendra 47 cas de TVP, 3 cas d'EP et 4 décès. Ainsi, l'augmentation estimative du coefficient coût-efficacité de l'enoxaparine s'établit à 29 120 $ par année de vie gagnée.

Conclusion : Selon les lignes directrices canadiennes en vigueur quant au coefficient coût-efficacité, les résultats de cette étude seraient considérés comme une indication variant de moyenne à forte en faveur de l'adoption d'une prophylaxie à l'enoxaparine contre la TVP après un remplacement total de la hanche. Or, à cause des données limitées, les estimations sont incertaines. Au cours d'études cliniques à venir, il faudrait comparer l'enoxaparine à la warfarine et y inclure une évaluation économique prospective.

Deep-vein thrombosis (DVT) is a common complication after orthopedic surgery of the lower extremities without prophylaxis. It develops in approximately 40% to 50% of patients after total hip replacement.[1] DVT is the source of over 90% of cases of pulmonary embolism (PE), which may be fatal in 1% to 3% of cases. In addition to the morbidity and mortality the diagnosis and treatment of DVT and PE consume valuable health care resources.

Several methods of prophylaxis against postoperative DVT are effective.[1,2] In a recent US survey warfarin was the most commonly used anticoagulant for DVT prophylaxis in hip surgery.[3] In a Canadian survey of 17 major orthopedic centres it was the drug of choice in 13 of the 16 centres where prophylaxis was used (Dr. K. Sue Robinson, Department of Medicine, Dalhousie University, Halifax: personal communication, 1993). However, a disadvantage of warfarin is inconvenience; blood levels must be carefully monitored and the dose adjusted to ensure optimal dosing.

Enoxaparin, licensed for use in Canada in 1993, is a low-molecular-weight heparin derivative obtained through chemical depolimerization of heparin. In a recent review of clinical trials enoxaparin was found to be more effective than standard heparin in preventing DVT when administered after total hip replacement and was associated with no greater risk of bleeding.[4] An advantage of enoxaparin is that it can be administered in a fixed twice-daily subcutaneous dose without the need for daily monitoring.

In addition to data on safety and efficacy, hospital and provincial formularies, in Canada[5] and elsewhere,[6] are requesting data on the cost-effectiveness of new drugs. Such economic data are particularly important in evaluating a drug such as enoxaparin because its acquisition cost of $19.55 per day is much higher than warfarin's cost of 30¢ per day.

We used available data to estimate the effectiveness, cost and cost-effectiveness of enoxaparin relative to low-dose warfarin. In the absence of clinical trials directly comparing enoxaparin and warfarin we estimated DVT rates from single arms of published randomized controlled trials through meta-analysis and used available literature to assess risks of PE and death. We used the framework of clinical decision analysis[7] to combine these data with cost data to estimate cost-effectiveness in terms of the expected cost per life-year gained by treatment.

Methods

Meta-analysis of efficacy

To determine rates of DVT with enoxaparin and warfarin prophylaxis we identified English-language reports of trials of prophylaxis against DVT published from January 1982 to December 1992. For inclusion in the meta-analysis studies had to meet the following criteria: (a) the study was a randomized controlled trial comparing enoxaparin or warfarin with any other prophylaxis against DVT in patients undergoing elective total hip replacement; (b) prophylaxis started no later than 24 hours after surgery and continued for at least 7 days; (c) the warfarin dose was adjusted to maintain a prothrombin time (PT) of 14 to 16 seconds, a prothrombin time ratio of 1.2 to 1.5 or an international normalized ratio of 2 to 3; (d) the enoxaparin dosage was 30 mg twice daily; (e) DVT was confirmed by bilateral venography.

Homogeneity of rates between studies was tested by χ^2 analysis. Overall risk of DVT with each drug was

estimated simply as the sum of events divided by the sum of patients at risk in the combined trials. Confidence intervals (CIs) were based on the formula for the variance of a proportion.[8]

Decision analysis of cost-effectiveness

Efficacy data from the prophylaxis trials have three limitations for use in the cost-effectiveness analysis. First, although venography is the diagnostic gold standard for diagnosing DVT in clinical trials, this invasive test is not the first-line diagnostic test in the routine management of patients. Second, not all cases of DVT detected by venography in trials will be clinically important and necessitate treatment. Third, the endpoints of DVT trials are intermediate health outcomes; the final outcomes are reductions in the risk of PE and death. In response to these problems we developed a decision analysis model of the prophylaxis, diagnosis and treatment of DVT and PE. Our model of typical patient management was based on opinion from a panel of six physicians experienced in the management of such patients at different centres across Canada.

The model is illustrated by the decision trees in Figs. 1 and 2, which provide separate analyses for enoxaparin and warfarin. The first branching in Fig. 1 reflects the known probability of DVT (from the trials). The four subsequent branches reflect the management of patients with and without DVT who receive clinical diagnoses that are true positive (branch 1), false negative (branch 2), false positive (branch 3) and true negative

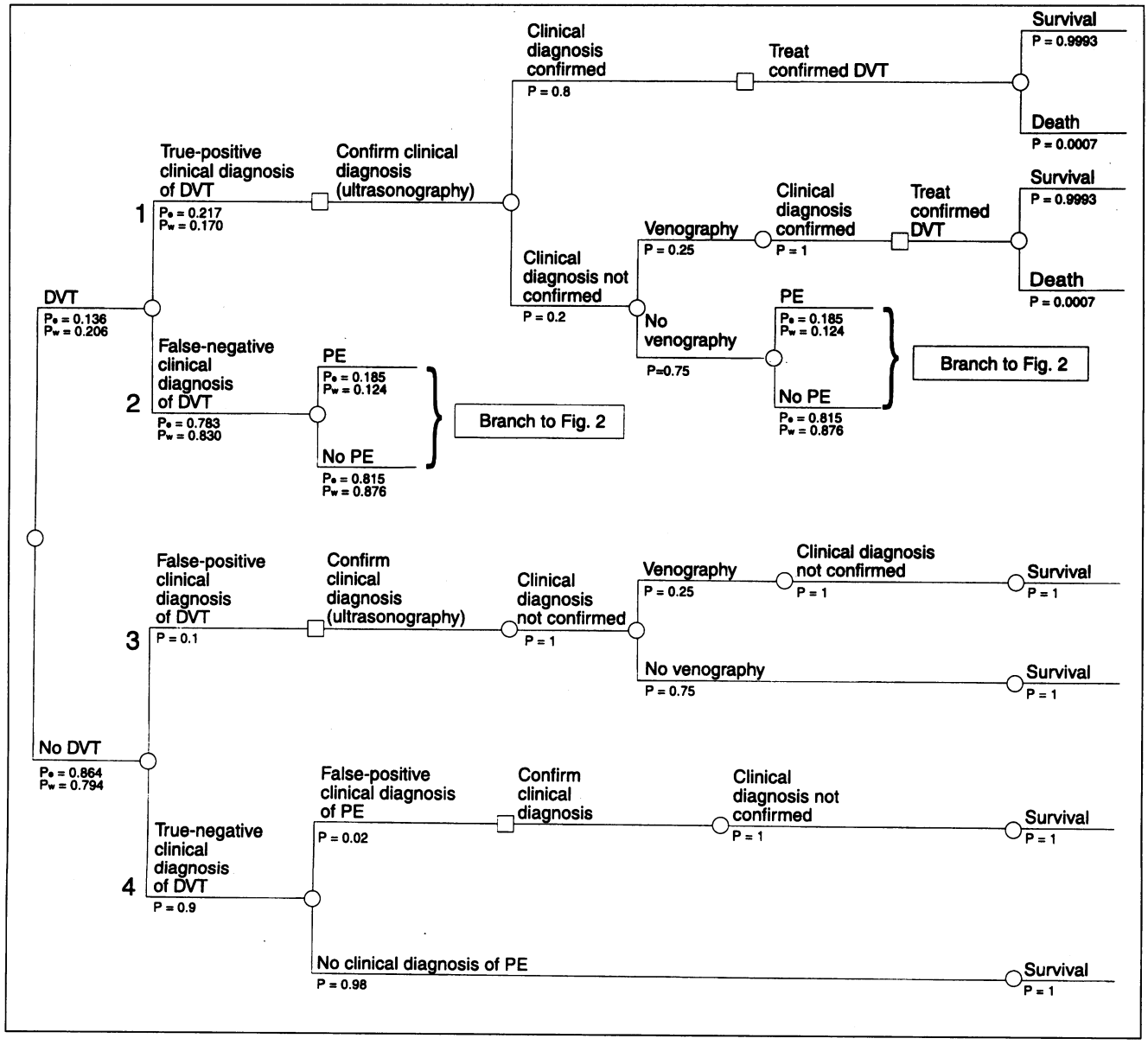

Fig. 1: Decision tree for diagnosing and managing deep-vein thrombosis (DVT). Squares denote choice nodes, and circles are chance nodes. Branches from chance nodes have associated probabilities that sum to 1 for each node. Probabilities specific to enoxaparin or warfarin regimen are denoted P_e and P_w respectively. PE = pulmonary embolism.

(branch 4). Clinical diagnoses are assumed to be confirmed or rejected by B-mode ultrasonography and venography. Fig. 2 then extends the decision tree for patients at risk of PE.

Clinical and diagnostic probabilities

In addition to DVT rates from the meta-analysis, data for clinical and diagnostic probabilities in the model were derived from the available literature on the natural history and diagnosis of DVT and PE. Key clinical probabilities were as follows.

Clinical diagnosis of DVT: About 5% of distal DVTs (in the calf) are clinically apparent, as compared with 40% of proximal DVTs,[9] and about 20% of distal DVTs will propagate to the proximal veins.[1] On the basis of these reports and the estimated rates of proximal and distal DVT from the meta-analysis we estimated that 22% of patients receiving enoxaparin and 17% of those receiving warfarin who have DVT would have had a true-positive clinical diagnosis. We assumed that 10% of patients who had a false-positive clinical diagnosis of DVT[1] would be excluded through diagnostic testing.

Sensitivity of B-mode ultrasonography: B-mode ultrasonography for diagnosing proximal DVT in symptomatic patients in hospital has been found to have a sensitivity of 89%[10] to 96%;[11] its sensitivity is likely to be lower for diagnosing distal DVT. Given that 90% of patients with clinically suspected DVT (Fig. 1, branch 1) will have proximal DVT we assumed an overall sensitivity for ultrasonography of 80%.

Death during treatment of confirmed DVT: Patients treated with anticoagulants such as intravenous heparin are at small risk of death from bleeding. Heparin trials[12–16] indicated that only 1 in 1400 patients treated died of bleeding (P = 0.0007).

PE: Reports in the literature indicated that 50% of undetected cases of proximal DVT develop into PE[17] and that 11% of these are fatal within the first hour.[18] Approximately 29% of patients who survive have their diagnosis confirmed by objective testing and receive anticoagulation therapy.[18] About 2.5% of these patients will die of PE.[19] Patients in whom PE is not clinically suspected are assumed to have a death rate of 30%.[19,20]

Discounted life expectancy: Data from the Hospital Medical Records Institute (HMRI) for 1990–91 indicate that the mean age of patients undergoing total hip replacement is 68 years.[21] In the absence of long-term survival data for such patients, we assumed that they would otherwise be in good health for their age and that, based on data from Canadian Life Tables,[22] they would live for another 15 years on average. Therefore, after a discounting of 5% per year[23] each death is associated with a loss of 10.38 years of life.

Costs of prophylaxis, diagnosis and treatment

The extent to which the occurrence of DVT or PE increases the length of hospital stay for a patient undergoing total hip replacement was estimated using HMRI data for 1990 and 1991 on 20 000 discharges for this indication.[21] The median length of stay for total hip replacement in the absence of DVT or PE is 13 days. If

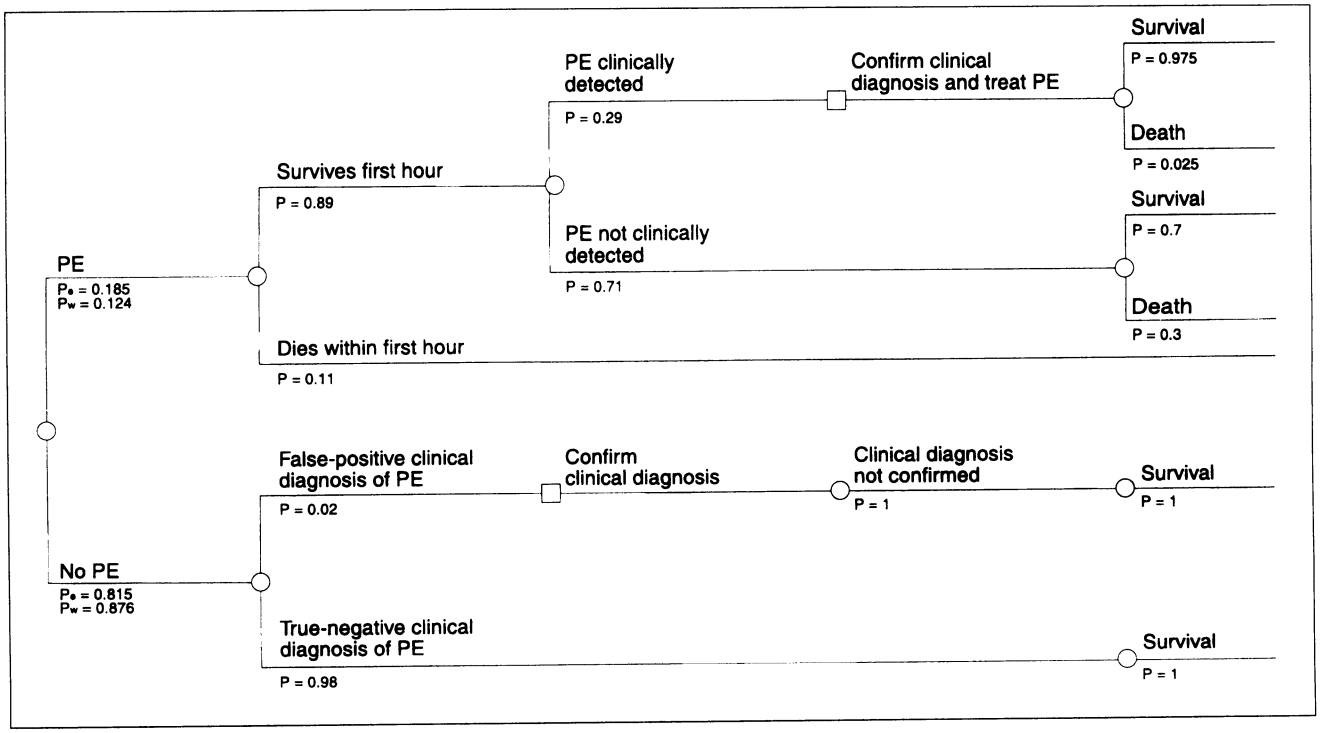

Fig. 2: Decision tree for diagnosing and managing PE.

DVT is the only thromboembolic complication the median length increases to 18 days (95% CI 17 to 19); if PE is an additional thromboembolic complication it increases to 20 days (95% CI 18 to 22).

We based the duration of prophylaxis on the observed length of stay from the HMRI data for hip replacement (without DVT or PE). We assumed that prophylaxis with enoxaparin (30 mg twice daily) would begin on day 3 of the hospital stay and be continued to day 13 (11 days of prophylaxis); we assumed that prophylaxis with warfarin would begin on day 2 (preoperative loading dose of 10 mg) and be continued to day 13. Patients receiving warfarin were assumed to have their prothrombin time monitored daily and the warfarin dose adjusted accordingly. Treatment of confirmed DVT or PE was assumed to be intravenous heparin (1000 U/h), continued for 5 days for patients with DVT and 7 days for those with PE.

We estimated costs of procedures and additional hospital stay using a corporate cost model for Chedoke–McMaster hospitals, in Hamilton, Ont.[24] Procedures such as ultrasonography have standard workload units assigned to them for management purposes;[25–27] the relation between expenditure and workload units can then be used to determine the cost of specific procedures. The cost of physician services was calculated from the physician fee schedule for Ontario.[28] For heparin and warfarin the costs were based on an informal survey of hospital pharmacies in Hamilton. Costs for prophylaxis, diagnosis and treatment are summarized in Table 1 (a more detailed account is available from the authors on request).

Cost-effectiveness analysis

The model was evaluated for a hypothetical cohort of 10 000 patients receiving either enoxaparin or warfarin. For each regimen we calculated the expected costs associated with prophylaxis, diagnosis and treatment of thromboembolic events, expected cases of confirmed DVT, expected cases of confirmed PE and expected deaths from PE. An incremental cost-effectiveness ratio was calculated from the ratio of the difference in cost to the difference in discounted life expectancy between enoxaparin and warfarin. Sensitivity analyses were undertaken to test the robustness of results under alternative assumptions.

Table 1: Costs of prophylaxis, diagnosis and treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE) after total hip replacement

Variable	Cost per patient, $*
Prophylaxis	
Enoxaparin, 11 d	244.76
Warfarin, 12 d	113.85
Diagnosis	
Confirming clinical diagnosis of DVT	481.26
Confirming clinical diagnosis of PE in patient	
With previous DVT	569.59
Without previous DVT	697.95
Treatment	
DVT (5 d in hospital, intravenous heparin therapy)	2031.88
PE (7 d in hospital, intravenous heparin therapy)	2887.59

*In 1992 Canadian dollars.

Results

Rates of DVT

Four trials of enoxaparin[29–32] (involving 567 patients) and six trials of warfarin[33–38] (involving 630) met the inclusion criteria for the meta-analysis. The trials and rates of DVT are presented in Table 2. The pooled rates of DVT overall and of distal DVT were lower with enoxaparin than with warfarin, and the 95% CI for rate differences did not include zero. For proximal DVT the difference in the pooled rates was not statistically significant at the 5% level. Test results of heterogeneity for overall rates of DVT were significant ($p < 0.05$) for the enoxaparin trials but not for the warfarin trials.

Expected costs and events

The expected cost per patient for prophylaxis, diagnosis and treatment of DVT and PE and the expected number of DVT events, PE events and deaths per 10 000 patients, according to our model, are presented in Table 3. The cost of enoxaparin prophylaxis per patient was more than twice that for warfarin ($245 v. $114). Given the greater efficacy of enoxaparin in preventing thromboembolic events, the expected cost for the diagnosis and management of DVTs and PEs was lower for patients receiving enoxaparin, by about $10 per patient. Overall, the avoided costs of DVT management achieved with enoxaparin were insufficient to offset the increased cost of prophylaxis; the enoxaparin regimen was expected to increase the cost per patient by $121.

The expected number of confirmed and treated cases of DVT per 10 000 patients was 251 with enoxaparin and 298 with warfarin. The efficacy of enoxaparin in reducing DVT incidence was reflected in three fewer cases of confirmed and treated PE and four fewer deaths than with warfarin.

Cost-effectiveness and sensitivity analysis

The incremental cost-effectiveness of enoxaparin relative to warfarin was estimated to be $29 120 per life-year gained (Table 3). Sensitivity analysis revealed that

results were most sensitive to alternative assumptions about enoxaparin efficacy. If the lower limit of the 95% CI for the overall rate of DVT with enoxaparin is used (10.9%) cost-effectiveness falls to $6000 per life-year gained; in contrast, the use of the upper limit (16.3%) favours warfarin, because enoxaparin becomes both less effective and more costly.

Discussion

In this study we used the limited available data to address a current question facing formulary decision-makers: the cost-effectiveness of a new drug. Our findings suggest that enoxaparin is more effective than warfarin in reducing overall rates of DVT (absolute risk reduction 7.1%), this effect being mainly restricted to reduced rates of distal DVT. Our model indicates that there will be three fewer cases of confirmed and treated PE and four fewer deaths per 10 000 patients treated with enoxaparin than with warfarin. But at a price of $19.55 per day enoxaparin prophylaxis will increase the cost per patient, even if the avoided costs of DVT and PE management are taken into account. We estimate that the additional cost per life-year gained with enoxaparin will be $29 120.

There are many threats to the validity of inferences drawn from meta-analyses of pooled data from multiple studies.[39] Our results should be viewed with caution because they do not summarize "head-to-head" trials of the

Table 2: Rates of DVT after total hip replacement from randomized, controlled trials of enoxaparin therapy and low-dose warfarin therapy

Trial	No. of patients	Location of DVT; no. (and %) of cases		
		Proximal	Distal	All
Enoxaparin				
Turpie et al, 1986[29]	30	1 (3.3)	2 (6.7)	3 (10.0)
Levine et al, 1991[30]	258	14 (5.4)	36 (14.0)	50 (19.4)
Spiro, 1991[31]	136	4 (2.9)	4 (2.9)	8 (5.9)
Spiro et al, 1992[32]	143	8 (5.6)	8 (5.6)	16 (11.2)
Pooled rate (and 95% CI*)		4.8 8.8 (3.0–5.6)	13.6 (6.5–11.1)	(10.9–16.3)
Warfarin				
Francis et al, 1983[33]	39	1 (2.6)	7 (17.9)	8 (20.5)
Paiement et al, 1987[34]	72	5 (6.9)	7 (9.7)	12 (16.7)
Bailey et al, 1991[35]	45	0	12 (26.7)	12 (26.7)
Kaempfe et al, 1991[36]	28	3 (10.7)	4 (14.3)	7 (25.0)
Francis et al, 1992[37]	103	3 (2.9)	20 (19.4)	23 (22.3)
Hull et al, 1992[38]	343	11 (3.2)	57 (16.6)	68 (19.8)
Pooled rate (and 95% CI)		3.7 (2.2–5.2)	17.0 (14.1–19.9)	20.6 (17.4–23.8)
Difference in pooled rate (and 95% CI)		+1.1 (−1.2–+3.4)	−8.2 (−11.9–−4.5)	−7.1 (−2.8–−11.2)

*CI = confidence interval.

Table 3: Expected costs, outcomes and cost-effectiveness of prophylaxis with enoxaparin and warfarin

Variable	Enoxaparin (E)	Warfarin (W)	Difference (E−W)
Cost per patient, $*			
Prophylaxis	245	114	+131
Diagnosis and treatment	110	120	−10
Total	355	234	+121
Outcome, no. of cases per 10 000 patients			
DVT†	251	298	−47
PE†	53	56	−3
Death	63	67	−4
Cost-effectiveness			
Cost per life-year gained, $‡	29 140	–	–

*In 1992 Canadian dollars.
†Confirmed and treated cases only; for DVT it was the only thromboembolic complication (i.e., no eventual PE).
‡Calculation = [121 ÷ (4 × 10.38)] × 10 000, where 121 is the expected increase in cost per patient given enoxaparin, 4 is the number of deaths, and 10.38 is the number of life-years lost per death.

two drugs and study populations may vary in their prior risk for DVT. Only two of the trials we reviewed directly compared low-dose warfarin and other types of low-molecular-weight heparin (logiparin[38] and RD-heparin[40]) in total hip replacement; both studies showed no difference in overall rates of DVT or of bleeding. Whether enoxaparin will be more efficacious or safer than other low-molecular-weight heparins is unclear.

We did not attempt to quantify the relative risks of bleeding associated with enoxaparin and warfarin, mainly because of the lack of standardized criteria for bleeding to permit meaningful comparisons between studies. Although some studies suggested that enoxaparin may result in fewer cases of bleeding than standard heparin[24] others have not confirmed this.[32] Furthermore, we did not consider DVT recurrence and the post-phlebitic syndrome after hospital discharge in our analysis. Inclusion of the costs and consequences of these complications would likely strengthen the case in favour of the drug with the lower incidence of DVT.

The study by Oster, Tuden and Colditz[1] demonstrated that prophylaxis against DVT in orthopedic surgery saves both lives and dollars. In this study we focused on the cost-effectiveness of enoxaparin versus warfarin in cases in which prophylaxis had been ordered. However, as discussed by Hirsh and Haynes,[41] despite consensus guidelines encouraging prophylaxis[2] this is not a universal practice. The availability of new anticoagulants that are more effective, safer or more convenient to use, or a combination of these features, may encourage more surgeons to use prophylaxis. This potential benefit of enoxaparin was not assessed in this study.

Is $29 120 per life-year gained with enoxaparin a good return on health care dollars? For a new drug to be cost-effective it does not have to save money, but the added benefits must be judged to be worth the added cost.[42] Ultimately this is a decision about what society is willing to pay to secure improved health benefits. The draft Ontario guidelines on the economic evaluation of pharmaceutical products[5] and a recent Canadian report[43] have attempted to construct guidelines concerning the strength of an economic case to adopt a new medical technology. For example, an intervention costing less than $20 000 per quality-adjusted life-year (QALY) is said to exhibit strong evidence for adoption, whereas one costing $20 000 to $100 000 exhibits moderate evidence for adoption. Interpreted in the framework of our study a cost of $29 120 per life-year gained would give moderate to strong evidence for adoption by current Canadian guidelines. However, we stress the uncertainty around our estimates because of the limited available data. We recommend that prospective trials be performed that directly compare enoxaparin and warfarin in terms of efficacy and cost-effectiveness.

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