Cost-effectiveness of enoxaparin compared with unfractionated heparin in ST elevation myocardial infarction patients undergoing pharmacological reperfusion: A Canadian analysis of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial

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OBJECTIVE: To evaluate the cost-effectiveness of enoxaparin versus unfractionated heparin in conjunction with fibrinolysis in ST elevation myocardial infarction patients within Canada.

DESIGN: Based on the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 trial, a model was created to analyze the cost-effectiveness of enoxaparin compared with unfractionated heparin in conjunction with fibrinolysis among ST elevation myocardial infarction patients within Canada. Clinical outcomes were derived from published results of the main trial. Resource use costs were first assessed based on United States Diagnosis-Related Group values for hospitalizations and Current Procedural Terminology codes for outpatient visits and tests. Both were then converted using Canadian local costs. Survival and life expectancy were estimated from Framingham survival data. The incremental cost-effectiveness ratio was expressed as cost per life year gained.

RESULTS: Through 30 days after random assignment, the primary composite end point favoured the enoxaparin group over the unfractionated heparin group (death or recurrent myocardial infarction rate 9.9% versus 12.0%, $P < 0.001$), and was associated with a modest increased cost of \$169.50 (\$8,757.00 versus \$8,587.50, respectively). Life years gained as a result of treatment with enoxaparin was increased by 0.11 years ($P < 0.05$). Enoxaparin was found to be cost-effective, as indicated by an incremental cost-effectiveness ratio of \$4,930 with a 99% probability of costing less than \$20,000.

CONCLUSIONS: Although associated with modest increased direct medication costs, enoxaparin following fibrinolysis improved the clinical efficacy in STEMI patients and increased the life years gained.

Key Words: Acute myocardial infarction; Anticoagulation; Clinical trials; Coronary artery disease; Cost-effectiveness

La rentabilité de l'énoxaparine par rapport à l'héparine non fractionnée chez des patients ayant subi un infarctus du myocarde avec élévation du segment ST qui reçoivent une reperfusion pharmacologique : Une analyse canadienne de l'essai sur l'énoxaparine et la reperfusion de la thrombolyse dans le traitement de l'infarctus aigu du myocarde – thrombolyse en cas d'infarctus du myocarde ExTRACT-TIMI 25

OBJECTIF : Évaluer la rentabilité de l'énoxaparine par rapport à l'héparine non fractionnée associée à la fibrinolyse chez des patients du Canada ayant subi un infarctus du myocarde avec élévation du segment ST.

MÉTHODOLOGIE : D'après l'essai sur l'énoxaparine et la reperfusion de la thrombolyse dans le traitement de l'infarctus aigu du myocarde – thrombolyse en cas d'infarctus du myocarde ExTRACT-TIMI 25, on a créé un modèle pour analyser la rentabilité de l'énoxaparine par rapport à l'héparine non fractionnée associée à la fibrinolyse chez les patients du Canada ayant subi un infarctus du myocarde avec élévation du segment ST. Les issues cliniques étaient dérivées des résultats publiés de l'essai principal. On a d'abord évalué les coûts d'utilisation des ressources d'après les valeurs du groupe lié au diagnostic des États-Unis pour les hospitalisations et les codes courants de terminologie des interventions à l'égard des consultations et des tests ambulatoires. On a ensuite converti les deux résultats au moyen des coûts canadiens locaux. On a évalué la survie et l'espérance de vie d'après les données de survie de Framingham. Le ratio de rentabilité incrémentielle était exprimé par le coût par année de vie gagnée.

RÉSULTATS : Dans les 30 jours suivant la répartition aléatoire, le paramètre ultime composite primaire favorisait le groupe prenant de l'énoxaparine par rapport au groupe prenant de l'héparine non fractionnée (taux de décès ou d'infarctus du myocarde récurrent de 9,9 % par rapport à 12,0 %, $P < 0,001$) et s'associait à une modeste augmentation des coûts de 169,50 \$ (8 757,00 \$ par rapport à 8 587,50 \$, respectivement). Les années de vie gagnées grâce au traitement à l'énoxaparine augmentaient de 0,11 an ($P < 0,05$). On a déterminé que l'énoxaparine était rentable, tel que l'indique le ratio coût-efficacité incrémentiel de 4 930 \$ et la probabilité à 99 % que les coûts soient inférieurs à 20 000 \$.

CONCLUSIONS : Quoiqu'elle s'associe à une augmentation modeste des coûts directs de médicaments, l'énoxaparine après la fibrinolyse améliorait l'efficacité clinique chez les patients ayant subi un infarctus du myocarde avec élévation du segment ST et accroissait les années de vie gagnées.

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In conjunction with fibrinolysis, adjunctive pharmacological therapy enhances the therapeutic effectiveness of pharmacological reperfusion. Adequate antiplatelet and antithrombotic therapy has been shown to contribute to the effectiveness of fibrinolysis by sustaining coronary artery patency and reducing the rate of repeat ischemic events following initial reperfusion with fibrinolysis (1-4). The Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment – Thrombolysis in Myocardial Infarction (ExTRACT-TIMI) 25 study randomly assigned patients to receive anticoagulation with either the low molecular weight heparin enoxaparin for the duration of hospitalization, or unfractionated heparin (UFH) administered for at least 48 h. A significant reduction in the primary end point of the 30-day death or repeat myocardial infarction (MI) rate was demonstrated with the enoxaparin-based strategy (5,6).

The objective of the present study was to examine the cost-effectiveness of enoxaparin compared with UFH in the context of treating ST elevation MI (STEMI) patients in Canada, using data from the ExTRACT-TIMI 25 study.

METHODS

ExTRACT-TIMI 25 study

The study was a prospective, randomized, double-blind, double-dummy, parallel group, multinational trial designed to compare enoxaparin and UFH as adjunctive therapies for fibrinolysis among patients with STEMI. Detailed descriptions of the trial design, inclusion and exclusion criteria, baseline characteristics, and results were previously published (5,6). Between October 24, 2002, and October 1, 2005, 20,506 eligible patients underwent random assignment at 674 sites in 48 countries (6). A total of 118 patients were randomly assigned within Canada.

UFH (or matching placebo) was administered as an intravenous bolus of 60 U/kg of body weight (maximum 4000 U) and an infusion of 12 U/kg/h (initial maximum 1000 U/h). The intravenous infusion was given for at least 48 h but could be continued for a longer period of time at the treating physician's discretion. The enoxaparin dosing strategy was adjusted according to the patients' age and renal function. For patients younger than 75 years of age, enoxaparin (or matching placebo) was given as a fixed, 30 mg intravenous bolus followed 15 min later by a subcutaneous injection of 1.0 mg/kg, with injections administered every 12 h. For patients who were at least 75 years of age, the intravenous bolus was eliminated and the subcutaneous dose was reduced to 0.75 mg/kg every 12 h. For the first two subcutaneous injections, a maximum of 100 mg (for patients younger than 75 years of age) or 75 mg (for patients 75 years of age or older) was administered. For patients with an estimated creatinine clearance of less than 30 mL/min, the dose was modified to 1.0 mg/kg every 24 h. The double-blind subcutaneous injections of enoxaparin or matching placebo continued until hospital discharge or for a maximum of eight days (whichever came first).

The primary efficacy end point was the composite of death from any cause or nonfatal recurrent MI in the first 30 days after random assignment. The main secondary end point was the composite of death from any cause, nonfatal reinfarction or recurrent myocardial ischemia leading to urgent revascularization in the first 30 days. An additional secondary end point (net clinical benefit) was the composite of death from any cause, nonfatal reinfarction or nonfatal disabling stroke.

Economic analysis

The economic evaluation was a cost-effectiveness analysis comparing enoxaparin with UFH using data from the ExTRACT-TIMI 25 trial, and applied to a 'typical' patient enrolled in the trial. The outcome measure for the cost-effectiveness analysis was life years gained (LYG). The time horizon for the analysis was 'lifetime' and results are expressed in 2004 Canadian dollars. While not all sources of costs could be accounted for, the overall perspective was societal.

Because cost-effectiveness ratios typically do not have a normal distribution, bootstrap methods with 5000 replicates (with replacement)

were used to estimate the distribution of costs and the incremental cost-effectiveness ratios (ICERs) (7). The joint distribution of cost and effectiveness were plotted in the cost-effectiveness plane. Quadrant I (northeast) of the cost-effectiveness plane indicates the new therapy is cost-effective (greater cost, but more effective) compared with current practice. Quadrant II (northwest) indicates the new therapy is dominant (less cost and more effective) compared with current practice. Quadrant III (southeast) also indicates that the new therapy is cost-effective (less cost) but less effective than the current practice. Quadrant IV (southwest) indicates dominance of the comparison group over the new therapy (ie, the new therapy costs more and is less effective). Evaluation of cost-effectiveness is dependent on the defined threshold; for the present study, the cost-effectiveness was set at \$20,000. A cost-effectiveness acceptability curve was plotted for a range of cost-effective thresholds ranging from \$0 to \$100,000. The discount rate recommended to be used in Canada is 5% for costs and benefits, to convert future cost and health outcomes to their current value, and to account for time preference and opportunity cost.

Costing

The costs accounted for in the present analysis are cost of treatment (enoxaparin or UFH), cost of index hospitalization, postdischarge to day 30 costs and long-term management (post day 30) costs.

The costs of enoxaparin and UFH were included in the analysis based on the observed use in the ExTRACT-TIMI 25 study. As per protocol, treatment with enoxaparin lasted a median of 7.0 days (interquartile range 4.5 to 7.5 days; 90th percentile 7.5 days) and treatment with UFH lasted a median of 2.0 days (interquartile range 2.0 to 2.2 days; 90th percentile 3.2 days). In the enoxaparin group, the initial bolus was 30 mg and the subsequent daily dose was 140 mg until hospital discharge (based on a median weight of 76 kg). It was assumed that the treatment was given for an average of seven days. In the UFH group, the initial bolus was assumed to be 4000 U, and the next infusion was 1000 U/h for 48 h. The Canadian unit prices for UFH and enoxaparin were \$0.0002982/U and \$0.204175/mg, respectively (8). The cost of treatment with enoxaparin was estimated to be \$206.22, while the cost of treatment with UFH was estimated to be \$15.51.

The index and subsequent hospitalizations for patients enrolled in the ExTRACT-TIMI 25 trial were assigned to a Diagnosis-Related Group in accordance with United States Medicare diagnostic standards. Outpatient procedures were coded by Current Procedural Terminology. Diagnosis-Related Groups and Current Procedural Terminology codes were translated into the Canadian Case Mix Group (CMG) system for costing in the Canadian health care system. Canadian unit costs, derived from the Ontario Case Costing Initiative, were applied to trial-based resource use to estimate treatment-specific 30-day medical costs (9). Thirty-day health care resource use was collected during the ExTRACT-TIMI 25 trial from individual patient history data. Data collected included details regarding the index hospitalization such as length of stay, major procedures and interventions (eg, cardiac catheterization, percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG], intra-aortic balloon pump, computed tomography scan and magnetic resonance imaging), resource use associated with severe adverse events, including bleeding, and information regarding rehospitalizations such as total length of hospital stay and per diem cost, and major procedures and interventions performed (eg, cardiac catheterization, PCI, CABG, intra-aortic balloon pump, computed tomography scan and magnetic resonance imaging).

Long-term management costs for patients surviving an MI were derived from the Canadian literature and were applied each year for the remaining lifetime of patients who survived beyond 30 days. Costs beyond one year through a lifetime were estimated for each study group as the average per capita national health expenditures in Canada of \$3,156 in 2004 (10). No data were available from the ExTRACT-TIMI 25 trial to calculate the costs of concomitant medication and indirect costs due to lost productivity.

TABLE 1
Resource use, unit costs and total costs associated with the index hospitalization

Description of resource	Canadian Case Mix Group code	Unit cost from OCCI, \$	Enoxaparin (n=10,256)		UFH (n=10,223)	
			Events, n	Cost of events*, \$	Events, n	Cost of events*, \$
Index hospitalization costs						
CABG surgery and percutaneous coronary intervention	179	19,417.09	2	3.80	6	11.40
CABG surgery and cardiac catheterization	178	33,479.38	160	522.30	141	461.80
CABG surgery	179	19,417.09	13	24.60	8	15.20
MI with major complications, discharged alive	205, 206, 207	7,958.59	531	412.10	568	442.20
MI without major complications, discharged alive	208	5,800.69	7036	3,979.50	6811	3,864.70
MI, deceased	CCI I210	12,963.83	570	720.50	618	783.70
Cardiac defibrillator implant without cardiac catheterization	186	14,775.82	28	40.30	19	27.50
Percutaneous coronary intervention	188,189	10,155.95	1899	1,880.50	2034	2,020.70
Cardiac defibrillator implant without cardiac catheterization with AMI/HF/shock	185	31,603.98	17	52.40	18	55.60
Total index hospitalization costs				7,635.90		7,682.70

Costs are presented in 2004 Canadian dollars. *Calculated as (the number of events / the total number of patients) $\times$ the unit cost of the event. AMI Acute myocardial infarction; CABG Coronary artery bypass graft; CCI Canadian Classification of Health Interventions; HF Heart failure; MI Myocardial infarction; OCCI Ontario Case Costing Initiative; UFH Unfractionated heparin

Life expectancy estimation

The ICER in terms of cost per LYG was estimated based on in-trial estimates of incremental costs, event rates (death, MI and stroke) and age-adjusted estimates of lost life expectancy associated with in-trial events (death, MI and stroke) obtained from the Framingham Heart Study (11,12). Life years lost (LYL) were calculated by subtracting the mean survival time given the observed pattern of events in the trial from the survival time expected, assuming no events occurred during the trial.

Briefly, the mean survival beyond the end of the trial was estimated by integrating the survival curves, adjusted for various patient characteristics, including experiencing specific subsequent ischemic events (13; abstract). Cox proportional hazards models for each time period were derived for patients. Age, diabetes, previous MI, previous ischemic stroke, previous CABG and lipid-lowering agent use were covariates (13-17). The cumulative survival functions over time were derived by applying the hazard functions in sufficiently brief intervals that the hazard could be assumed to be constant over the time period.

Estimates of LYL due to events were obtained by subtracting life expectancy estimates for individuals with a given event pattern from life expectancy estimates for individuals with no events (18). This assumed that nonfatal events in the trial had the same prognostic importance as events from the Framingham database. For patients who experienced multiple events of different types during the trial, lost life expectancy was estimated assuming a hierarchy of death, stroke and MI (eg, the lost life expectancy of patients with both nonfatal MI and nonfatal stroke was based on estimates for patients with nonfatal stroke). The difference between treatment groups in average LYL due to events (UFH minus enoxaparin) yielded an estimate of the LYG with enoxaparin. LYL was discounted 5% annually after the first year.

Thirty-day survival and medical resource use data for enoxaparin and UFH were derived directly from the ExTRACT-TIMI 25 trial to inform the analysis. Canadian life expectancy data for a survivor of MI was used to extrapolate survival beyond 30 days (10).

Marginal time costs were used to examine the impact of in-trial costs on the future medical costs based on the different treatments in the trial. In the economic analysis, one of the basic assumptions was that all medical costs would be the same except for in the following two aspects: in the 30-day trial, because different treatments were accepted at difference prices; and in costs associated with LYL, which is based on the length of LYL and the health expenditure per capita. The marginal time cost for each treatment group is the difference between the total in-trial costs and the costs associated with LYL. Therefore, marginal time cost illustrates the influence of in-trial costs

on the lifetime medical costs, which are the long-term economic effects of the different treatments in the trial. The marginal time cost discrepancy of two treatment groups was defined as the difference between the in-trial cost (30-day cost in the present study) and the cost associated with LYL gained.

Sensitivity analysis

Registries and clinical trials demonstrate a median duration of hospitalization of approximately five days for Canadian STEMI patients (19-21). Thus, a sensitivity analysis was conducted in which the duration of hospitalization and thus, the duration of follow-up infusion, were assumed to be five days. Other sensitivity analyses were performed by assuming an additional 10% to 40% increase or decrease of LYL for enoxaparin and UFH.

RESULTS

The primary efficacy end point (30-day death or nonfatal MI) rate was 9.9% in the enoxaparin group, compared with 12.0% in the UFH group (17% reduction in RR, $P<0.001$) (6). The beneficial effect of enoxaparin on the primary end point was consistent across key pre-specified subgroups including those who underwent PCI within 30 days after random assignment (23% reduction in RR) or who were treated medically (16% reduction in RR, $P=0.33$ for interaction) (6,22).

Costs include those incurred during the index hospitalization and following discharge to 30 days. The index hospitalization costs of each treatment group are presented in Table 1 based on the Canadian CMGs and related frequency of occurrence. These costs were estimated to be \$7,635.90 in the enoxaparin group and \$7,682.70 in the UFH group. The costs of resources used in the postdischarge period until day 30 are presented in Table 2. These costs were estimated to be \$832.00 in the enoxaparin group and \$795.30 in the UFH group. Costs related to outpatient tests and procedures accounted for \$82.90 in the enoxaparin group and \$94.00 in the UFH group (Table 3).

The 30-day cost, marginal time cost and LYL are presented in Table 4. Total 30-day costs were \$8,757.00 for enoxaparin and \$8,587.50 for UFH (\$169.50 higher for enoxaparin). The total marginal time costs were \$6,417.60 for enoxaparin and \$5,888.70 for UFH. LYG as a result of treatment with enoxaparin were significantly increased by 0.11 years ($P<0.05$). When considering the marginal time horizon and allowing clinical benefit to be accounted for, enoxaparin was found to be cost-effective, as indicated by an ICER of \$4,930 and a 99% probability of the cost-effectiveness ratio being less than \$20,000 (5000 bootstrap replicates) (Table 5 and Figure 1).

TABLE 2
Resource use, unit costs and total costs associated with subsequent hospitalizations

Description of resource	Case Mix Group code	Unit cost from OCCl, \$	Enoxaparin (n=10,256)		UFH (n=10,223)	
			Events, n	Cost of events*, \$	Events, n	Cost of events*, \$
Subsequent hospitalization costs						
Intracranial hemorrhage and stroke with infarct	I64	8,189.33	9	7.20	20	16.00
Other disorders of the eye, age >17 years, with CC	0.987 (US DRG cost)	5,419.21	1	0.50	0	0
Pulmonary embolism	220	6,290.99	3	1.80	1	0.60
Pleural effusion with CC	J90	7,295.19	1	0.70	2	1.40
Pulmonary edema and respiratory failure	141, 136	20,381.43	2	4.00	1	2.00
Simple pneumonia and pleurisy, age >17 years without CC	143	6,284.43	0	0	1	0.60
Other respiratory system diagnoses without CC	147	4,541.52	0	0	1	0.40
CABG and PCI	179	19,417.09	1	1.90	2	3.80
CABG and cardiac catheterization	178	33,479.38	21	68.60	17	55.70
Other cardiothoracic procedures	181, 182	26,104.65	2	6.60	0	0
CABG only	179	19,417.09	110	208.30	111	210.80
MI with major complications, discharged alive	205, 206, 207	7,958.59	5	3.90	5	3.90
MI without major complications, discharged alive	208	5,800.69	57	32.30	50	28.40
MI, deceased	CCI I210	12,963.83	19	24.00	9	11.40
Heart failure	222	7,364.49	69	49.50	68	49.00
Deep vein thrombophlebitis	895	5,421.27	1	0.50	1	0.50
Peripheral vascular disorders without CC	898	6,195.28	1	0.60	2	1.20
Atherosclerosis with CC	229	4,444.82	0	0	1	0.40
Hypertension	233	3,342.29	3	1.00	3	1.00
Cardiac congenital and valvular disorders, age >17 years without CC	234	3,146.19	1	0.30	0	0
Cardiac arrhythmia and conduction disorders without CC	237	4,412.24	10	4.30	12	5.20
Angina pectoris	235	2,717.27	151	40.00	131	34.80
Syncope and collapse without CC	240	3,178.43	2	0.60	0	0
Chest pain	242	2,483.09	0	0	2	0.20
Other circulatory system diagnoses without CC	226	6,039.10	4	2.40	8	4.70
Bleeding (major and minor): complication of treatment with CC	T810	3,541.66	15	5.20	7	2.40
Rehabilitation	841	8,431.52	7	5.80	9	7.40
Cardiac defibrillator implant without cardiac catheterization	186	14,775.82	1	1.40	3	4.30
PCI	188, 189	10,155.95	358	354.50	351	348.70
Cardiac defibrillator implant with cardiac catheterization with AMI/HF/shock	185	31,603.98	2	6.20	0	0
Total index hospitalization costs				832.00	795.30	

Costs are presented in 2004 Canadian dollars. *Calculated as (the number of events / the total number of patients) × the unit cost of the event. AMI Acute myocardial infarction; CABG Coronary artery bypass graft surgery; CC Cardiac catheterization; CCI Canadian Classification of Health Interventions; HF Heart failure; MI Myocardial infarction; OCCI Ontario Case Costing Initiative; PCI Percutaneous coronary intervention; UFH Unfractionated heparin; US DRG United States Diagnosis-Related Group

Sensitivity analysis

Reducing the treatment duration of enoxaparin to five days reduced the treatment cost to \$147.30, thereby reducing the treatment cost difference to \$126.09. This brings the ICER down to \$1,176/LYG. Marginal time costs were then varied by ±15%, and LYL from ±10% to ±40%. A decrease of 15% in marginal time costs resulted in an ICER of \$4,191; an increase of 15% resulted in an ICER of \$5,670 (Table 5). Figure 2 plots ICERs in LYG ranging from −40% to +40%.

DISCUSSION

The recent ExTRACT TIMI-25 trial demonstrated that enoxaparin is superior to UFH in the adjuvant antithrombin treatment of STEMI (6). A significantly greater reduction in the combined 30-day all-cause mortality and nonfatal MI (primary end point) rate as well as the combined 30-day all-cause mortality, nonfatal recurrent MI and urgent

revascularization (secondary end point) rate of patients receiving enoxaparin compared with those receiving UFH was demonstrated.

The present Canadian economic evaluation has shown the cost-effectiveness of enoxaparin over UFH as adjuvant antithrombin therapy to fibrinolysis for STEMI. Although the direct medication cost of enoxaparin was higher than UFH as delivered in the ExTRACT-TIMI 25 trial, the enoxaparin strategy was associated with improved clinical efficacy, which decreased the need for other procedures, many of which are costly, thus achieving cost-effectiveness. The main driver of the economic evaluation was the impact of the difference in survival between enoxaparin and UFH. In the base-case analysis, adjuvant treatment with enoxaparin, compared with UFH, resulted in an increase of 0.11 years of life per patient. This was attained at a higher cost of \$528.80 per patient. The difference in total costs between treatment arms was driven

TABLE 3
Resource use, unit costs and total costs associated with outpatient tests and procedures

Description of resource	Current Procedure Terminology code	Unit cost from OCCI, \$	Enoxaparin (n=10,256)		UFH (n=10,223)	
			Events, n	Cost of events*, \$	Events, n	Cost of events*, \$
Outpatient test/procedure costs						
Computed tomography (head scan)		755.46	1	0.07	1	0.07
Magnetic resonance imaging (head scan)		1,286.93	124	15.60	143	18.00
Transcatheter placement of an intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel	1IJ50GQBD, 1IJ50GQOA	6,883.23	63	32.30	66	33.90
Cardiac catheterization	3IP10VC, 3IP10VX	1,822.08	197	35.00	234	41.70
Electrophysiology studies	2HZ24GPKL, 2HZ24HAXJ, 2HZ24JAKE, 2HZ24JAKH, 2HZ24JAKP, 2HZ24JAKT, 2HZ24JAXJ	928.05	0	0	1	0.30
Total outpatient test/procedure costs				82.90	94.00	

Costs are presented in 2004 Canadian dollars. *Calculated as (the number of events / the total number of patients) × the unit cost of the event. OCCI Ontario Case Costing Initiative; UFH Unfractionated heparin

TABLE 4
Thirty-day and marginal time costs, and life years lost (LYL)

	Enoxaparin	UFH	Difference (enoxaparin – UFH)	95% CI
30-day costs, \$				
Treatment	206.22	15.51	190.71	–
Index hospitalization	7,635.90	7,682.70	–46.70	–154.30 to 68.50
Subsequent hospitalization	832.00	795.30	36.70	–55.90 to 126.60
Subsequent outpatient procedure	82.90	94.00	–11.10	–26.80 to 6.80
Total	8,757.00	8,587.50	169.50	28.80 to 310.30
Marginal time costs*, \$				
Costs associated with LYL	2,339.50	2,698.80	–359.30	–580.60 to –137.90
Total marginal time costs	6,417.60	5,888.70	528.80	301.00 to 756.70
LYL (5% discount)	0.6984	0.8057	0.1072 [†]	0.0410 to 0.1731

*The average per capita participant Canada national health expenditures of \$3,165 in US\$ in 2004 and the conversion factor of 1.05693 (for July 11) were used (ie, CAD\$3,345); [†]The difference in LYL was calculated as unfractionated heparin (UFH) minus enoxaparin

TABLE 5
Cost-effectiveness and sensitivity analyses for a marginal time horizon

Item	Costs, \$		Enoxaparin – UFH		ICER	% dominated	% dominant	% <\$20,000/LYG
	Enoxaparin (n=20,256)	UFH (n=20,223)	Difference, \$	LYG				
30 days	8,757.00	8,587.50	\$169.50	0.1072	1,580.6	<0.1	0.1	99
Marginal time	6,417.50	5,888.70	528.80	0.1072	4,930.4	<0.1	0.1	99
5-day enoxaparin treatment	8,713.60	8,587.50	126.10	0.1072	1,176.2	<0.1	0.1	99
Marginal time –15%	5,454.90	5,005.40	449.50	0.1072	4,190.9	<0.1	0.2	99
Marginal time +15%	7,380.10	6,772.00	608.10	0.1072	5,670.1	<0.1	<0.1	99

ICER Incremental cost-effectiveness ratio; LYG Life years gained; UFH Unfractionated heparin

primarily by the difference in drug therapy costs, which were higher in the enoxaparin arm. The analysis found a very favourable cost per LYG of \$4,930 for enoxaparin compared with UFH. These results are consistent with a recent analysis also based on ExTRACT-TIMI 25 using a United States model of health economics (23).

By using a threshold value of \$20,000 per LYG, the estimated probability that enoxaparin is cost-effective compared with UFH is 99%, suggesting that enoxaparin represents an efficient use of health care resources. These results are consistent with those drawn from other studies assessing the cost-effectiveness of adjuvant antithrombin therapy with enoxaparin in fibrinolysis for both STEMI and non-STEMI patient populations (24,25).

The extrapolation of survival beyond 30 days assumes that the life expectancy of patients after 30 days is similar between patients receiving enoxaparin and those receiving UFH. A post-MI specific life expectancy of 15 years was used based on published literature (26). The assumption of equivalent life expectancy assumes that the difference in survival between arms of the study does not widen or close after 30 days. Long-term clinical data are required to confirm this assumption.

Limitations

There are certain limitations to the present economic analysis. The extrapolation of survival beyond 30 days assumes that the

Figure 1) Scatter plot of the joint distribution of cost and effectiveness differences in the cost-effectiveness (CE) plane and acceptability curve for the Marginal time analysis. ICER Incremental cost-effectiveness ratio; UFH Unfractionated heparin

life expectancy after 30 days is similar between patients receiving enoxaparin and those receiving UFH. A post-MI specific life expectancy of 15 years was used based on published literature (26). The assumption of equivalent life expectancy assumes that the difference in survival between arms of the study does not widen or close after 30 days. Long-term clinical data are required to confirm this assumption. Second, the 30-day costs were based on pooled resource use reported in the ExTRACT-TIMI 25 trial, which reflect United States practice patterns for hospitalization and treatment. In the present analysis, reported trial resource use was combined with average costs derived from 2004 Canadian sources. If estimates of resource use were available locally, the cost-effectiveness results would certainly show some variation, primarily because of the resources used within the 30-day duration of the trial. Furthermore, additional costs associated with nursing time, requirements for intravenous tubing and blood testing for activated partial thromboplastin time specific to UFH were not

Figure 2) Sensitivity analyses. Enoxaparin has an additional 10% to 40% increase or decrease of life years gained compared with unfractionated heparine (UFH) (assuming a utility of 0.8 for the ST elevation myocardial infarction patients). ICER Incremental cost-effectiveness ratio; QALY Quality-adjusted life years

available. Also, despite detailed information supplied regarding resources used in the present trial, some information was not available, including missing admission and/or discharge dates, for some hospitalizations. However, for scenarios in which costs were increased by 25% and decreased by 25%, the impact on the ICERs was minimal. Third, the analysis excluded the cost of subsequent cardiovascular events from the base-case analysis, due to a lack of information regarding the incidence of these events in patients with STEMI. Based on limited data regarding the rate of subsequent MI among patients with STEMI, we determined that the impact of excluding these costs was minimal. Finally, we took into account the cost of treatment separate from the CMGs. Therefore, the methodology used may have induced double counting of the antithrombotic treatment since the cost of such treatment may already have been included in the calculation for CMGs. However, because the same CMG costs were used for both the enoxaparin and UFH groups, and because only the incremental costs were taken into account, the double counting would not have affected the incremental cost calculation or the ICER.

CONCLUSIONS

Enoxaparin is cost-effective compared with UFH in adjuvant treatment of patients receiving fibrinolysis for STEMI, based on an analysis of 30-day data from the ExTRACT-TIMI 25 trial, and extrapolation of outcomes and costs over a lifetime. Therefore, in patients with STEMI undergoing pharmacological reperfusion, the strategy of administering enoxaparin during the period of hospitalization or until day 8, consistent with the ExTRACT study design, is attractive. This remains true with the provision that the dose adjustments used in the trial for the elderly and those with renal impairment are followed carefully, and that clinical judgment continues to guide the duration of anticoagulation following PCI, which may occur more frequently following fibrinolysis in Canada than in the overall ExTRACT TIMI-25 study.

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