Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cost-effectiveness of Dalteparin vs Unfractionated Heparin for the Prevention of Venous Thromboembolism in Critically Ill Patients

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IMPORTANCE Venous thromboembolism (VTE) is a common complication of acute illness, and its prevention is a ubiquitous aspect of inpatient care. A multicenter blinded, randomized trial compared the effectiveness of the most common pharmocoprevention strategies, unfractionated heparin (UFH) and the low-molecular-weight heparin (LMWH) dalteparin, finding no difference in the primary end point of leg deep-vein thrombosis but a reduced rate of pulmonary embolus and heparin-induced thrombocytopenia among critically ill medical-surgical patients who received dalteparin.

OBJECTIVE To evaluate the comparative cost-effectiveness of LMWH vs UFH for prophylaxis against VTE in critically ill patients.

DESIGN, SETTING, AND PARTICIPANTS Prospective economic evaluation concurrent with the Prophylaxis for Thromboembolism in Critical Care Randomized Trial (May 2006 to June 2010). The economic evaluation adopted a health care payer perspective and in-hospital time horizon; derived baseline characteristics and probabilities of intensive care unit and in-hospital events; and measured costs among 2344 patients in 23 centers in 5 countries and applied these costs to measured resource use and effects of all enrolled patients.

MAIN OUTCOMES AND MEASURES Costs, effects, incremental cost-effectiveness of LMWH vs UFH during the period of hospitalization, and sensitivity analyses across cost ranges.

RESULTS Hospital costs per patient were $39 508 (interquartile range [IQR], $24 676 to $71 431) for 1862 patients who received LMWH compared with $40 805 (IQR, $24 393 to $76 139) for 1862 patients who received UFH (incremental cost, −$1297 [IQR, −$4398 to $1404]; P = .41). In 78% of simulations, a strategy using LMWH was most effective and least costly. In sensitivity analyses, a strategy using LMWH remained least costly unless the drug acquisition cost of dalteparin increased from $8 to $179 per dose and was consistent among higher- and lower-spending health care systems. There was no threshold at which lowering the acquisition cost of UFH favored prophylaxis with UFH.

CONCLUSIONS AND RELEVANCE From a health care payer perspective, the use of the LMWH dalteparin for VTE prophylaxis among critically ill medical-surgical patients was more effective and had similar or lower costs than the use of UFH. These findings were driven by lower rates of pulmonary embolus and heparin-induced thrombocytopenia and corresponding lower overall use of resources with LMWH.

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Thromboprophylaxis is a key component of care for critically ill patients because of their high risk of venous thromboembolism (VTE) and because heparin is an effective and safe prevention strategy. The Joint Commission now specifies thromboprophylaxis as a key quality measure for hospitalized patients.[1] A recent multicenter blinded, randomized trial (PROTECT [Prophylaxis for Thromboembolism in Critical Care Trial]) compared the effectiveness of the 2 most common pharmocoprevention strategies, administration of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH). Results of the trial included no difference in the primary end point of leg deep-vein thrombosis (DVT) but reduced rates of pulmonary embolus and heparin-induced thrombocytopenia in the patients who received LMWH.[2]

Drug acquisition costs have historically been higher for LMWH than for UFH. However, if the effects of these drugs on outcomes important to patients differs substantially, paying more may be worth it, and this highlights the need for comparative economic and clinical effectiveness research to inform practice. There is considerable variability in current prescribing patterns.[3-5] Although LMWH is more commonly used in Europe,[6,7] cost is cited as the most important barrier to using LWMH in a recent North American survey.[8] Accordingly, we conducted a prospective economic evaluation concurrent with PROTECT to measure costs at participating centers. We related these costs to clinical outcomes and complications to determine the economic consequences of these 2 prevention strategies in critically ill medical-surgical patients.

Methods

Design

Our primary objective was to compare the clinical and economic outcomes of the LMWH dalteparin compared with UFH for the prevention of VTE in critically ill medical-surgical patients. We developed our analysis according to previously existing guidelines for economic evaluations[9-11]; however, we used an in-hospital health care payer perspective to encompass all hospital costs, including physician and other personnel costs. PROTECT provided follow-up for patients until death or discharge from the hospital; therefore, our time horizon was from the period of randomization to hospital discharge or death.

Our analysis plan was prespecified as part of the economic evaluation of the PROTECT protocol before trial completion and unblinding (clinical trials.gov NCT00182143).[2,12,13] All centers participating in this economic evaluation obtained research ethics approval to enroll patients in the trial, approval to include non-patient-based costing data, or both. All patients provided written informed consent for enrollment in the trial.

Patients

PROTECT was an international randomized trial in which patients, clinicians, and adjudicators were blinded. Critically ill medical-surgical patients received thromboprophylaxis comprising either once-daily subcutaneous dalteparin (5000 U) and placebo or twice-daily subcutaneous UFH (5000 U). Inclusion and exclusion criteria have been described.[2] In summary, patients were at least 18 years old, weighed at least 45 kg, had an expected intensive care unit (ICU) stay of 72 hours or more, and were eligible to receive LMWH or UFH. We excluded patients who had absolute contraindications to pharmacologic thromboprophylaxis, had allergy to study drug, or had an established indication for either therapeutic anticoagulation or a particular agent.[14] From May 2006 to June 2010, 3746 patients were enrolled in PROTECT, with all costs collected during the same period; 1873 were allocated to dalteparin, and 1873 to UFH. No patients were lost to follow-up. The main analyses were based on the intention-to-treat principle, which also informed the clinical events and costs measured in the economic analyses.[2,13]

Effects

We recorded the frequency of DVT, pulmonary embolus, major bleeding, and suspected and confirmed heparin-induced thrombocytopenia among all patients in PROTECT. The primary clinical outcome was the difference in any VTE (all limb DVT, pulmonary embolus, and nonlimb thromboses). Secondary clinical outcomes were episodes of DVT, pulmonary embolus, major bleeding, and heparin-induced thrombocytopenia avoided. Tertiary clinical outcomes included death in ICU and in hospital; however, PROTECT was designed and powered to evaluate differences in the rate of thrombotic events between 2 thrombosis prevention strategies, not differences in life expectancy. Given an in-hospital time horizon and focus on thrombotic and bleeding events, we did not directly measure short-term health-related quality of life.

Costs

We developed lists of costs by performing a systematic review of the VTE and critical care cost-effectiveness literature.[15] The steering committee reviewed evidence underlying the relative importance of cost variables and performed a pilot study to determine feasible and optimal mechanisms of determining these costs for PROTECT patients in different health care systems.[12] Finding various system-specific methods to calculate patient-specific total costs and charges during the ICU and hospital admission, we elected to standardize measurement of individual resource unit costs for critically ill patients enrolled in PROTECT by using a standardized cost × utilization approach for each patient, to approximate total inpatient costs from the time of randomization until discharge from hospital or death.

Patient costs were collected for 2344 patients (1169 in the LMWH group, 1175 in UFH group) enrolled in a subset of 23 of the 67 hospitals in 5 of 6 countries participating in PROTECT (Canada, 12; Australia, 5; United States, 3; Saudi Arabia, 2; Brazil 1). All centers were invited to participate in the costing component of the economic evaluation. Participating centers were self-selected but reflect overall proportions of patients enrolled in PROTECT among all participating countries. Costs were captured in the following

categories: drugs, laboratory tests, personnel, diagnostic testing, procedures and operations, bleeding and blood product transfusion services, and infrastructure (eMethods in the Supplement).[12,13,16-20]

Institution-specific costs were requested from participating centers; if charges were known, we converted to costs by using the institution's cost-to-charge estimate for that item. Professional costs (performance, interpretation, or both) and technical costs were recorded for procedures when applicable. We used median values to mitigate the influence of high and low cost outliers but also present arithmetic mean costs to calculate total per-group cost. All individual costs were updated to reflect end-of-trial costs, and country- and year-specific costs were then converted to 2013 dollars, accounting for annual inflation and then converting to US currency.[21-23] We used international currency conversion instead of purchase power parity (PPP)-based conversions because health-specific PPPs were not available for all participating countries, and nonhealth PPP conversion rates varied substantially over the period of the analysis.[13] As of June 1, 2013, US $1 was worth approximately 1.03 Canadian dollars, 1.04 Australian dollars, 2.12 Brazilian real, and 3.75 Saudi Arabian riyal.[21-23]

Analytic Plan

The a priori planned base-case cost-effectiveness ratio was the ratio of incremental costs per incremental effects of LMWH over UFH during the period of hospitalization. At the patient level, individual variable costs were multiplied by the frequency or event rates for medications administered, laboratory and radiological tests incurred, other diagnostic or therapeutic procedures performed, transfusions received, per-day personnel costs, and ICU or ward costs. Total costs for each of the LMWH and UFH groups were calculated by summing each individual patient cost. Incremental costs were taken as the difference in per-patient costs between groups. Incremental effects were defined as the difference in per-patient event rates between groups. For the scenario of improved effects with higher costs, we planned to calculate incremental cost-effectiveness ratios (cost to prevent a thrombosis at any site; cost to prevent a pulmonary embolus, DVT, major bleeding event, or episode of heparin-induced thrombocytopenia), as is commonly used in cost-effectiveness analysis of VTE prevention.[15] However, for the situation of similar or improved effects and smaller costs, a cost-minimization approach was taken by comparing incremental cost (savings) alone.

We used descriptive analyses with counts (and proportions), means (with SDs), or medians (with interquartile ranges [IQRs]) to describe baseline characteristics, effects, and costs. We tested differences in costs and effects using standard parametric or nonparametric tests (χ^2 tests, 2-sample *t* tests, and Wilcoxon rank sum tests) as appropriate. We directly calculated the incremental cost difference and generated 95% CIs, using the bias corrected and accelerated method in R version 2.14.1 (R Foundation for Statistical Computing), among 10 000 bootstrap samples.[24,25] Statistical significance for differences among a priori comparisons was set at $P = .05$ (2-sided).

Subgroups

We investigated specific subgroups of patients in PROTECT, including medical vs surgical patients, patients with high vs low illness severity at admission (Acute Physiology and Chronic Health Evaluation II score ≥25 vs <25), body mass index (≥40 vs <40, calculated as weight in kilograms divided by height in meters squared), and patients who received inotropes or vasopressors at admission vs those who did not.

Sensitivity Analyses

Because patient characteristics, effects, and costs may differ outside clinical trials and in various jurisdictions, we prospectively planned a sensitivity analysis to explore how incremental cost-effectiveness ratios may change with plausible differences in costs of LMWH and UFH. We performed 10 000 bootstrap simulations in the following manner: each simulation drew 1862 patients per group, with replacement (for both events and cost) in pairs. For each sample, the difference in event rate and cost was calculated, obtaining 10 000 pairs of differences in cost and event rate to generate an incremental cost-effectiveness plot (**Figure**).[26,27] We performed a 2-way sensitivity analysis varying the cost of LMWH simultaneously with the daily cost of care in the ICU (institutional and personnel costs) across plausible ranges to explore potential cost differences in higher- and lower-spending health care systems. We explored the influence of differential rates of pulmonary embolus on costs between patients receiving LMWH and UFH by randomly removing 19 patients with pulmonary embolus from the UFH group (the between-group difference in event rate) and repeated this procedure 1000 times to obtain median (IQR) costs adjusting for the differential rate of pulmonary embolus. We performed additional analyses reflecting country-specific costs and effects and also analyses from the lifetime and societal perspective using a modified model previously described by our research team.[28]

Oversight

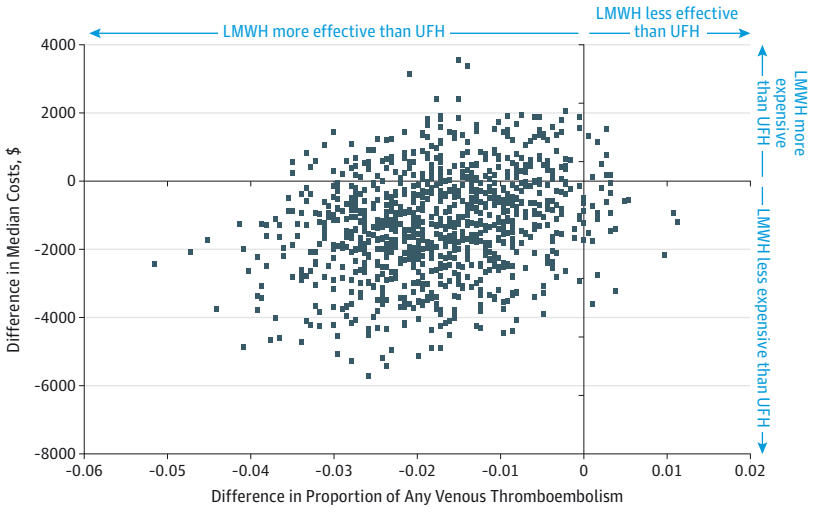
Study operations, methods, submission for funding, and manuscript generation were coordinated by the Economic Evaluation of the PROTECT steering committee (R.F., N.M., D.C., W.G., M.G., M.K., G.G.).

Results

Characterics of Study Population

Patient characteristics of the economic evaluation of the PROTECT trial are the same as those of the trial (3746 patients randomized to the LMWH dalteparin [1873] or UFH [1873]). The mean age was 61 years, 57% were men, 76% were admitted to the ICU for medical critical illness, and 90% required mechanical ventilation (eTable 1 in the Supplement). There were 22 patients (11 in each group) who, after randomization, were discovered to have exclusion criteria and were excluded from further daily data collection;however, these patients were not lost to follow-up and were included in the intention-to-treat analysis.[2] Therefore, 1862 patients in each group were used to determine resource use and cost calculations.

Figure. Incremental Cost-effectiveness for Low-Molecular-Weight Heparin (LMWH; as Dalteparin) vs Unfractionated Heparin (UFH)



Horizontal axis indicates difference in proportions between the 2 study drug venous thromboembolism rates; vertical axis, the difference in costs for the 2 compared strategies, across all patients in PROTECT.

Clinical Effects

As previously reported,[2] there were no statistically significant differences in rates of any thrombosis, DVT, and major bleeding; however, there were fewer episodes of pulmonary embolus and confirmed heparin-induced thrombocytopenia among patients who received dalteparin (eTable 2 in the Supplement). Median duration of mechanical ventilation, ICU and hospital stay, and ICU and hospital mortality were similar.

Resources and Costs

Table 1 outlines medications used, transfusions received, laboratory and radiologic investigations performed, procedures performed for trial-related effects, complications, and personnel and institution resources consumed during the ICU stay, until death or hospital discharge.

There was variable use of nonheparin anticoagulants between groups, corresponding to numerically more cases of suspected, and significantly more confirmed, cases of heparin-induced thrombocytopenia in the group that received UFH (Table 1). Among patients receiving UFH, there were more episodes of any thrombosis, significantly more patients with pulmonary embolus (eTable 2 in the Supplement), and more VTE-related diagnostic imaging (Table 1). Therefore, this group also received more therapeutic anticoagulation, including transition to warfarin, during their hospital stay (Table 1). There were no differences in major bleeding rates between groups (eTable 2 in the Supplement) and no differences in related procedures or transfusions (Table 1). Patients who developed VTE or bleeding in the ICU had substantially increased duration of ICU and hospital stay as compared with those who did not (eTable 3 in the Supplement), and, although median durations of stay in ICU and hospital were not statistically different between groups (eTable 2 in the Supplement), patients who received UFH had more days in the ICU and hospital (Table 1), with corresponding greater group personnel and fixed daily hospital costs (unrelated to patient-specific medication, testing, diagnostic imaging, procedures, or personnel). **Table 2** lists costs for medications, transfusions, laboratory and radiologic investigations, procedures, personnel, and additional daily institution costs.

Cost Comparisons Between Patients Who Received UFH or Dalteparin

The total cost incremental difference between groups was $2 773 635, favoring dalteparin. Among all patients, the median postrandomization hospital costs of care for patients who received UFH was nonsignificantly greater ($40 805 [IQR, $24 393-$76 139] per patient) (mean cost, $63 290 per patient; total costs, $117 845 793) compared with $39 508 (IQR, $24 676-$71 431 per patient) (mean cost, $61 800 per patient; total cost, $115 072 158) for patients who received dalteparin (median difference, −$1297 [95% CI, −$4398 to $1404]; $P = .41$; mean cost difference, −$1490; $P = .53$) and associated with nonsignificantly greater rates of thrombosis and bleeding (**Table 3**). Thus, LMWH was the dominant prevention strategy.

Subgroup Analyses

In 7 of 8 prespecified subgroups according to medical vs surgical status, illness severity by Acute Physiology and Chronic Health Evaluation II score, body mass index, and baseline receipt of vasopressors or inotropes, costs were numerically but nonsignificantly lower for patients who received dalteparin (**Table 4**). Using conventional cost metrics to prevent specific VTE-related events,[15] dalteparin was the dominant strategy to prevent all thrombotic events, pulmonary embolus, DVT, major bleeding, and heparin-induced thrombocytopenia, given its lower cost combined with better effects (Table 4).

Sensitivity Analyses

Although cost determinations were made for 23 centers in 5 countries, costs for specific components of care may differ in certain jurisdictions. We first examined the relative influence of all individual costs using a Tornado diagram (eFigure 1 in

Table 1. Study Medications, Laboratory and Radiological Tests, Transfusions, and Procedures

Resources	Heparin	
	Unfractionated (n = 1862)	Low-Molecular-Weight (n = 1862)
Medications, Doses		
Unfractionated heparin[a]		
Prevention	69 493	36 316
Treatment	2372	1911
Low-molecular-weight heparin[a]		
Prevention	2984	19 700
Treatment	788	648
Danaparoid		
Prevention	116	45
Treatment	6	5
Warfarin	3809	3162
Fondaparinux	54	109
Argatroban	33	110
Lepirudin	22	76
Proton pump inhibitors	19 040	18 257
Intravenous vasoactive medications, d	1054	997
Laboratory HIT tests, No.[b]	397	366
Radiologic investigations, No.		
Extremity ultrasound	6285	6088
CT scan and angiogram (lungs)	81	73
CT scan (VTE-related, other)	16	6
Echocardiogram (VTE-related)	6	2
Ventilation-perfusion scan	2	3
Transfusion (all)	2056	1910
Red blood cells, U	1720	1533
Plasma, U	217	251
Cryoprecipitate, U	11	18
Platelets (5 units)	108	108
Procedures, No.		
Angiogram and embolization	7	10
Diagnostic endoscopy	105	103
Vena cava filter insertion	16	12
Dialysis	283	309
Surgery		
Laparotomy for exploration of bleeding or thrombosis	22	16
Personnel		
ICU		
Physician, nurse, pharmacist, respiratory therapist, clerical d[c]	26 517	25 757
Consultant physician visits	606	524
Social work visits	1873	1873
Ward		
Physician, nursing, pharmacist, clerical d[c]	41 214	41 086
Social work encounters	1569	1589
Mechanical ventilation, d		
Invasive	17 495	16 346
Noninvasive	321	390
Institution Days		
ICU		
First d	1862	1862
Days after first d	24 644	23 884
Ward, all d	41 214	41 086

Abbreviations: CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; VTE, venous thromboembolism.

[a] Dalteparin administered once daily and unfractionated heparin administered twice daily, resulting in numerically greater doses of unfractionated heparin for trial-related prophylaxis. Among patients who had thromboses or who had HIT that required therapeutic or prophylactic anticoagulation, these medications received outside the ICU were assumed to be the same as those received in the ICU, with a transition to warfarin after 3 days on the ward and a completed transition by day 6. For other patients without thrombosis or HIT in the ICU we assumed that VTE prophylaxis on medical and surgical wards was provided with unfractionated heparin because it was not directly measured outside of ICU and represented the most common usual strategy in centers.

[b] Includes a combination of a screening (eg, ELISA EIA-G) test followed by a confirmatory (eg, serotonin release assay) test.

[c] Represents the number of days that patients received care from each of the listed personnel.

the Supplement) and found that higher per-day institutional and personnel costs were the largest contributors to between-group differences in costs of care. Costs for patients who received dalteparin remained lower than for UFH when varying daily institutional costs, personnel costs, transfusion costs, surgery and diagnostic imaging, screening for heparin-induced thrombocytopenia, and confirmatory testing costs across interquartile ranges, or ±25% when cost distributions were uncertain. Because drug acquisition costs may vary substantially across jurisdictions, we explored the threshold at which the drug acquisition costs of dalteparin and UFH would lead to greater overall costs for dalteparin. Dalteparin was the least costly strategy until its acquisition cost rose from a base case cost of $8 to $179 per dose (eFigure 2 in the Supplement). There was no threshold in which lowering the acquisition cost of UFH favored this prophylactic strategy. Using a probabilistic sensitivity analysis, dalteparin was more effective and less expensive than UFH in 78% of simulations (Figure), and VTE prophylaxis with LMWH was associated with cost savings in both higher- and lower-spending health care systems (eFigure 3 in the Supplement). These findings, from the in-hospital time-horizon and health care system payer perspective, were consistent with a modeled lifetime horizon from a societal perspective[28] and when country-specific costs and effects were used (eTables 4, 5A, 5B in the Supplement). Adjusting for between-group differences in pulmonary embolus, we found a median cost per patient of $40 633 (IQR, $24 366-$75 759) for UFH, compared with $39 508 (IQR, $24 676-$71 431) for LMWH, indicating cost savings beyond the reduction in pulmonary embolus rate alone.

Table 2. Costs Associated With Care for Critically Ill Patients Treated With Unfractionated Heparin and Low-Molecular-Weight Heparin

Variable	Cost, Median (IQR), US $[a]
In-Hospital Unit Costs	
Medications (per patient and per specified dose)	
Unfractionated heparin (5000 IU twice daily)	3 (1-4)
Dalteparin (5000 IU once daily)	8 (7-8)
Warfarin (5 mg enterally)	0.27
Pantoprozole (40 mg daily, intravenous)	14
Lepirudin (100-150 mg daily, intravenous, treatment dosing)[b]	377
Argatroban (81 mg daily, intravenous, treatment dosing)[b]	663
Danaparoid (3750 U daily, intravenous, treatment dosing)[b]	120
Fondaparinux (7.5 mg subcutaneously, treatment dosing)[b]	26
Epinephrine infusion (eg, 10 µg/min or 14.4 mg daily, intravenous)	23
Laboratory testing (per test)	
ELISA (EIA-G) screening and serotonin release assay confirmation test	220 (186-245)
Radiologic investigations (per test)	
Extremity ultrasound	120 (95-324)
CT scan and angiogram (lungs)	135 (96-486)
Ventilation-perfusion scan	254 (241-422)
Echocardiogram	302
CT Scan (VTE-related, other)	123 (123-393)
Transfusions (units)	
Red blood cells (1)	431
Plasma (1)	188
Cryoprecipitate (1)	30
Platelets (5)	538
Procedures (per procedure)	
Angiogram and embolization	404
Diagnostic endoscopy	206 (162-307)
Vena cava filter insertion	1925 (1901-1997)
Dialysis, intermittent or continuous per day	1201
Laparotomy for exploration of bleeding or thrombosis	1178
Personnel, ICU (per patient per d)	
Critical care physician	
Day 1	332 (326-343)
Days 2-30	218 (183-224)
Day 30 onward	87
Consultant physician	
Initial visit	141 (77-154)
Follow-up	39 (31-40)
Nursing (per d)	847 (803-947)
Respiratory therapy (per d)	111 (103-137)
Pharmacy (per d)	24 (21-27)
Social work (per ICU stay)	160 (98-175)
Clerical staff (per d)	20 (20-21)
Personnel, Ward (per patient per d)	
Physician	
Day 1	141 (77-154)
Day 2 onward	39 (31-40)
Nursing (per d)	169 (161-189)
Pharmacy (per d)	24 (21-27)
Social work (per ward stay)	160 (98-175)
Clerical staff (per d)	10.07 (10.07-10.29)
Institutional Resources and Fixed Costs (per patient per d)[c]	
ICU	
Day 1	2671.15 (2020.66-3039.44)
Day 2 onward	1671.97[b]
Ward, day 1 onward	668.79[b]

Abbreviations: CT, computed tomography; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; ICU, intensive care unit; IQR, interquartile range; SRA, serotonin release assay; VTE, venous thromboembolism.

[a] Costs are displayed as median and IQR wherever possible. Some costs are represented with single values when they are derived from microcosting studies at a single center. Costs are in US dollars as of 2013.

[b] Lepirudin loading dose (0.2 mg/kg [15 mg] intravenous), followed by 0.05 mg/kg per hour (3.75 mg/h; 90 mg/d), at $104 per 50-mg vial, requiring on average 3 to 4 vials per day. Attributable costs, from Nanwa et al,[18] 2009: $377 per day (2011). Argatroban (0.75 µg/kg per minute [81 mg/d] × 5 d (or 405 mg) at $663 for 250 mg/2.5 mL). Attributable costs, from Nanwa et al,[18] 2009: $663 per day (2011). Danaparoid treatment loading dose (2250 units intravenously), then 400 U/hour × 4 hours, then 300 U/hour × 4 hours followed by 200 U/hour for a patient weighing 70 to 75 kg, leading to 6000 U on day 1 and 3750 U days 2 through 5, at 750 U/ampule and $20/ampule, or approximately $120 per day for a 5-day course. Attributable costs from Nanwa et al, 2009.[18]

[c] Intensive care unit day 1, day 2, and ward days are calculated from a ratio of 4:2.5:1, respectively, applied using all centers' intensive care unit day-1 fixed costs.

Table 3. In-Hospital Costs and Effectiveness of Venous Thromboembolism Prevention With UFH vs LMWH (Dalteparin)

	Median, $		Incremental Cost, Effect, $[a]	*P* Value
	UFH	LMWH		
Costs per patient	40 805	39 508	−1297	.41
All thrombotic events	186	154	−32	.24
Pulmonary embolism	43	24	−19	.01
Deep venous thrombus	161	138	−23	.54
Major bleeding event	105	103	−2	.98
Heparin-induced thrombocytopenia	12	3	−9	.16

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

[a] Negative values of costs and effects favor LMWH, the dominant strategy (more effective and less expensive than UFH).

Discussion

In this prospective economic evaluation, conducted parallel to PROTECT, we found that prevention of VTE using the LMWH dalteparin was not more expensive than UFH and was associated with similar rates of DVT, lower rates of pulmonary embolus, and less heparin-induced thrombocytopenia. Sensitivity analyses demonstrated that a strategy using LMWH was most effective, least costly 78% of the time, and remained least costly unless the drug acquisition cost of dalteparin was to increase by more than 20-fold. There was no threshold in which lowering the acquisition cost of UFH favored prophylaxis with UFH.

These findings are important for the care of critically ill patients because they provide a cost-minimization rationale that complements clinical effectiveness knowledge from PROTECT. For example, if an ICU with 1000 medical-surgical admissions per year uses UFH instead of LMWH for prevention of VTE, the annual incremental cost may be between $1 000 000 to $1 500 000 with similar or worse clinical outcomes, despite the individual drug cost of UFH being $4 to $5 less per day.

Our findings complement prior systematic reviews and guidelines of the literature related to effectiveness and cost-effectiveness of VTE prevention.[15,29,30] Both the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines and the United Kingdom National Health Service VTE Prevention Guidelines, completed before publication of PROTECT, recommend either LMWH or UFH for critically ill medical-surgical patients and recommend LMWH for those at highest risk of VTE, including those who have orthopedic, neurosurgical, or pregnancy-related illness.

This economic evaluation highlights that use of LMWH for VTE prophylaxis may be less costly than use of UFH. Although a recent systematic review of prior VTE economic evaluations in hospitalized patients found that LMWH and fondaparinux were the most economically attractive VTE prevention strategies, no randomized trials have evaluated fondaparinux prophylaxis during critical illness.[15] Recent evidence from acutely ill and traumatically injured patients also indicates that nonpharmacological prophylaxis with vena caval filters is likely associated with substantially increased risk of thrombotic and nonthrombotic complications and increased cost.[31,32]

Sensitivity analysis indicates the relative importance of various factors in the incremental cost differences between strategies, especially length of stay in the ICU and hospital, with attendant personnel and indirect costs being most influential. Reductions in VTE radiologic diagnostic tests, vena cava filter insertions, the diagnosis and treatment of heparin-induced thrombocytopenia, and subsequent bleeding-related treatment complications also led to lower costs among patients receiving VTE prophylaxis with LMWH. The suspicion and confirmed diagnosis of heparin-induced thrombocytopenia represent a substantial clinical burden for patients and cost burden for payers[18] in addition to the potential for medicolegal costs, which were not captured in our study. This economic analysis emphasizes that prophylaxis with LMWH may be one mechanism to minimize such risk and potential health care system expenditures.

Strengths of this study include the prospective design and collection of prespecified costs in study centers alongside a randomized, blinded trial. Most other economic analyses have been retrospectively designed and analyzed after results of the primary trial were known.[15] In the current study, effects and costs were based on actual patient-level data, not on a decision-analytic model with hypothetical cohorts and data integrated from other literature that may be less representative of the relevant groups in this comparison. Further, cost and effects had known distributions and variance in this analysis, allowing a more precise estimate of between-group differences than with most economic analyses. Our study was not funded by the manufacturer of either LMWH or UFH.

This economic analysis is limited in that the results are dependent on cost estimates at the time of the trial; analyses may change if costs change substantially over time. However, a threshold analysis demonstrating that LMWH was least costly unless the drug acquisition cost increased from $8 to $179 per dose, and the absence of a threshold in the acquisition cost of UFH, makes our findings robust to drug cost modifications. Costs vary across various health care systems, and cost savings will be accrued by different payers or providers (hospitals, clinicians) depending on the system; for example, if hospitals are provided a fixed global budget or are reimbursed according to a diagnosis related group, cost savings will be accrued by the hospital. Subgroup analysis, however, did not reveal differences among countries or higher- and lower-

Table 4. Per-Patient, Total, and Incremental Costs Among Patients Treated With UFH vs LMWH (Dalteparin)[a]

	Group			
	UFH	LMWH	Difference	*P* Value
All Patients				
No.	1862	1862		
Cost per patient, median (IQR), $	40 805 (24 393 to 76 139)	39 508 (24 676 to 71 431)	−1297 (−398 to 1404)	.41
APACHE II Score				
<25				
Patients, No.	1223	1242		
Cost per patient, median (IQR), $	37 955 (23 039 to 69 230)	37 848 (23 230 to 66 564)	−107 (−2396 to 2218)	.66
≥25				
Patients, No.	638	619		
Cost per patient, median (IQR), $	48 373 (28 007 to 83 916)	44 009 (28 239 to 83 624)	−4364 (−9983 to 711)	.48
BMI[b]				
<40				
Patients, No.	1674	1663		
Cost per patient, median (IQR), $	40 971 (24 695 to 76 176)	39 584 (24 818 to 71 230)	−1387 (−4504 to 1366)	.36
≥40				
Patients, No.	126	133		
Cost per patient, median (IQR), $	46 231 (28 261 to 87 606)	42 755 (26 612 to 76 094)	−3476 (−15 767 to 9222)	.41
Baseline Vasopressors				
Yes				
Patients, No.	872	805		
Cost per patient, median (IQR), $	45 769 (27 303 to 83 237)	43256 (27 947 to 79 440)	−2513 (−6468 to 958)	.43
No				
Patients, No.	990	1057		
Cost per patient, median (IQR), $	37 184 (22 696 to 66 668)	37 525 (22 765 to 65 743)	341 (−2292 to 2786)	.89
Care Type				
Medical				
Patients, No.	1413	1400		
Cost per patient, median (IQR), $	40 096 (24 033 to 74 762)	39 163 (24 363 to 70 943)	−933 (−4002 to 1703)	.69
Surgical				
Patients, No.	449	462		
Cost per patient, median (IQR), $	44 483 (25 617 to 81 547)	40 457 (26 353 to 72 852)	−4026 (−8493 to 1421)	.29

Abbreviations: APACHE, Acute Physiology and Chronic Health Examination; BMI, body mass index; IQR, interquartile range; LMWH, low-molecular-weight heparin (dalteparin); UFH, unfractionated heparin.

[a] One patient was withdrawn from study at day 70 while still in the intensive care unit and final status information could not be collected; therefore, day 70 was designated the patient's intensive care unit and hospital discharge day. One patient was still in the hospital when the database was closed on January 24, 2011 (approximately 10 months after randomization). We used that day as the patient's intensive care unit and hospital discharge day.

[b] Calculated as weight in kilograms divided by height in meters squared.

spending health care systems. Nonetheless, our findings require real-world contextualization according to the costing and payment systems in each setting.

This analysis was based on the measures of efficacy from a clinical trial as opposed to effectiveness under real-world conditions. However, the eligibility criteria for PROTECT led to participation of a broadly representative population of critically ill patients. Additionally, the prespecified subgroup analyses did not reveal substantial differences among more specific populations. Certain study-related procedures such as baseline and biweekly screening leg ultrasounds for DVT outcome assessment do not represent usual practice. Although such protocolized ultrasounds do have an associated cost and are not recommended for routine practice,[32] they were equal in number across the 2 groups and had no effect on differential costs. By contrast, differential rates of VTE led to more nonprotocolized diagnostic ultrasounds and cost in the UFH group.

In PROTECT, the numbers of heparin-induced thrombocytopenia and pulmonary embolus events were small, allowing only moderate confidence in estimates of superiority with LMWH. In this study, cost differences with LMWH were driven by apparent decreases in all thrombosis and heparin-induced

thrombocytopenia and between-group differences in length of stay and accompanying resource use. In primary and secondary analyses, the differences in incremental effects and costs favored LMWH; however, costs were not statistically significantly different between groups. In part, this may relate to limited power to demonstrate significant differences among only 23 centers; however, country-specific analyses of costs and effects revealed no country-specific differences in findings (eTables 4, 5A, 5B, and 6 in the Supplement). As well, our costing methods were chosen after a pilot study revealed substantial variation in center-specific costing methodologies, and we opted for a more standardized—and likely more conservative—costing approach in this analysis. Although our methods attempted to estimate total costs of care after randomization, it is likely that some were not captured.

Further, our analyses were based on an in-hospital time-horizon (as opposed to lifetime) and were performed from the health care payer (as opposed to societal) perspective. Both were prespecified to focus on the effect- and cost-data–rich period of ICU and hospital admission. We did not incorporate health-related quality-of-life estimates in the form of measured utilities attributable to the in-hospital time horizon and focus on objective thrombotic events and their complications. However, findings from the in-hospital time horizon and health care system payer perspective are consistent with a previously modeled lifetime horizon from a societal perspective using data from PROTECT and E-PROTECT that show a favorable incremental cost-effectiveness ratio for LMWH compared with UFH.[28]

PROTECT compared a single LMWH, dalteparin, with UFH, and our findings may not be generalizable to all LMWHs in this drug class. For example, although prophylactic doses of dalteparin have been shown safe and effective in patients with renal failure,[33] other LMWHs may not have the same pharmacokinetic profile. However, existing observational evidence suggests a class effect for VTE prevention, and our threshold analysis indicates that even LMWHs with a higher drug acquisition cost are likely to represent an economically favorable strategy.

Conclusions

From a health care payer perspective, VTE prophylaxis with the LMWH dalteparin in critically ill medical-surgical patients was more effective and had similar or lower costs than the use of UFH. These findings were driven by lower rates of pulmonary embolus and heparin-induced thrombocytopenia and corresponding lower overall use of resources with LMWH.

ARTICLE INFORMATION

Author Contributions: Dr Fowler had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
Study concept and design: Fowler, Mittmann, Geerts, Gould, Guyatt, Krahn, Cook.
Acquistion, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
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