

ORIGINAL RESEARCH

Comparative Effectiveness of Low-Molecular-Weight Heparin Versus Unfractionated Heparin for Thromboembolism Prophylaxis for Medical Patients

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BACKGROUND: Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are approved for venous thromboembolism (VTE) prophylaxis. Which agent is superior remains controversial.

OBJECTIVE: To compare the effectiveness, complications, and costs of UFH and LMWH as VTE prophylaxis for hospitalized medical patients.

DESIGN: Retrospective cohort.

SETTING: Three hundred thirty-three acute care facilities in 2004–2005.

PATIENTS: Adults with 4 common medical diagnoses considered to carry moderate-to-high risk of VTE. Excluded were patients on warfarin or with hospital stays of ≤ 2 days. VTE prophylaxis was assessed from billing data.

INTERVENTION: None.

MEASUREMENTS: VTE, major bleeding or heparin-induced thrombocytopenia, mortality, and cost.

RESULTS: Of 32,104 patients who received prophylaxis, 55% received LMWH and the remainder received UFH. The hospital where the patient obtained care was the strongest predictor of receiving LMWH. VTE was observed in 163 (0.51%) patients; complications, followed by stopping therapy, were rare ($<0.2\%$). In analysis adjusted for the propensity for UFH and other covariates, patients treated with UFH had an odds ratio for VTE of 1.04 (95% confidence interval [CI] 0.76 to 1.43) compared to LMWH. In a grouped treatment model, the odds of VTE with UFH was 1.14 (95% CI 0.72 to 1.81). Adjusted odds of bleeding with UFH compared to LMWH were 1.64 (95% CI 0.50 to 5.33), adjusted odds of complications followed by stopping prophylaxis were 2.84 (95% CI 1.43 to 45.66), and adjusted cost ratio was 0.97 (95% CI 0.90 to 1.05).

CONCLUSIONS: For VTE prophylaxis, the effectiveness and cost of LMWH and UFH are similar, but LMWH is associated with fewer complications. *Journal of Hospital Medicine* 2012;7:457–463. © 2012 Society of Hospital Medicine

Venous thromboembolism (VTE) is a major source of morbidity and mortality for hospitalized patients, with as many as 16% of high-risk medical patients developing VTE during their hospital stay.^{1,2} Pharmacologic prophylaxis with subcutaneous heparin reduces the risk of VTE by approximately 50%,^{3,4} and guidelines produced by the American College of Chest Physicians (ACCP) recommend thromboprophylaxis for patients at moderate-to-high risk of VTE with either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH).² UFH is less expensive per dose, but meta-analyses have suggested that UFH may be either less effective than LMWH³ or more likely to cause complications, such as bleeding⁵ or heparin-induced thrombocytopenia (HIT).⁶ Others

have argued that the efficacy and risk of bleeding with UFH and LMWH are similar.^{7,8} In either case, there are few head-to-head studies of LMWH and UFH in medical patients and they tend to be small. In the most recent meta-analysis, which included fewer than 4500 patients, several different low-molecular-weight heparins were assessed together, and the observed rate of deep vein thrombosis (DVT) with UFH was high (5.4%), with evidence suggesting publication bias.³

Given the current Joint Commission requirement⁹ that all medical patients either receive VTE prophylaxis or have documented a reason not to, the implications related to choosing one form of VTE prophylaxis over another are substantial on a national scale. In order to compare the effectiveness of UFH and LMWH in routine practice among hospitalized medical patients, we conducted a retrospective cohort study in a national sample of hospitals and compared the risk of VTE, bleeding, HIT, and death associated with each treatment.

METHODS

Setting and Patients

We conducted a retrospective cohort study of patients discharged between January 1, 2004 and June 30,

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Additional Supporting Information may be found in the online version of this article.

Received: November 7, 2011; Revised: January 31, 2012; Accepted: February 1, 2012

2012 Society of Hospital Medicine DOI 10.1002/jhm.1938

Published online in Wiley Online Library (Wileyonlinelibrary.com).

2005 from 333 acute care facilities in the United States that participated in Premier's Perspective, a database we have described previously.¹⁰ Compared to US hospitals as a whole, Perspective hospitals are more likely to be located in the South and in urban areas. Perspective contains the following data elements: sociodemographic information, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, as well as a list of all billed items with a date of service, including diagnostic tests, medications, and other treatments. Hospitals' characteristics include size, region, setting, and teaching status. The Institutional Review Board at Baystate Medical Center granted permission to conduct the study (#132280-1).

We included general medical patients aged ≥ 18 years whose ICD-9-CM primary diagnosis code (congestive heart failure, stroke, pneumonia, and urinary tract infection) placed them at moderate-to-high risk of VTE according to the ACCP recommendations,² and who received daily prophylactic dosages of either LMWH (40 mg daily) or UFH (10,000–15,000 units daily) initiated by hospital day 2 and continued to discharge or until the patient developed a VTE or a complication attributable to heparin. Patients were included so long as they missed no more than 1 day of prophylaxis or had no more than 1 unusual dose recorded. Patients who switched between heparin types were included and analyzed according to their initial therapy. Patients who received any other regimen were excluded. We also excluded patients who received warfarin on hospital day 1 or 2, because they would not be considered candidates for heparin prophylaxis, and patients whose length of stay was ≤ 2 days, because the value of VTE prophylaxis in such cases is unknown.

Data Elements

For each patient, we extracted age, gender, race, and insurance status, principal diagnosis, comorbidities, and specialty of the attending physician. Comorbidities were identified from ICD-9-CM secondary diagnosis codes and Diagnosis Related Groups using Healthcare Cost and Utilization Project Comorbidity Software, version 3.1, based on the work of Elixhauser and colleagues.¹¹ We also identified additional risk factors for VTE using a combination of ICD-9-CM codes and specific charges. These included cancer, chemotherapy/radiation, prior VTE, use of estrogens and estrogen modulators, inflammatory bowel disease, nephrotic syndrome, myeloproliferative disorders, smoking, central venous catheter, inherited or acquired thrombophilia, mechanical ventilation, urinary catheter, decubitus ulcer, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, restraints, and varicose veins. Hospitals were categorized by region (Northeast, South, Midwest, or West), bed size, setting (urban vs rural), and teaching status.

Outcome Variables

We defined hospital-acquired VTE as a secondary diagnosis of VTE (ICD-9-CM diagnoses 453.4, 453.40, 453.41, 453.42, 453.8, 453.9, 415.1, 415.11, 415.19), combined with a diagnostic test for VTE (lower extremity ultrasound, venography, computed tomography (CT) angiogram, ventilation-perfusion scan, or pulmonary angiogram) after hospital day 2, followed by treatment for VTE (intravenous unfractionated heparin, >60 mg of enoxaparin, ≥ 7500 mg of dalteparin, or placement of an inferior vena cava filter) for at least 50% of the remaining hospital days or until initiation of warfarin or appearance of a complication (eg, transfusion or treatment for heparin-induced thrombocytopenia). We chose this definition to differentiate hospital-acquired VTE from VTE present on admission.¹² In addition, patients who were readmitted within 30 days of discharge with a primary diagnosis of VTE were also considered to have hospital-acquired VTE.

We also assessed complications of VTE prophylaxis. Major bleeding was defined as the receipt of 2 or more units of packed red blood cells on a single day or a secondary diagnosis of intracranial bleeding. Because there was no ICD-9-CM code for HIT, we assessed codes for all thrombocytopenia, as well as secondary thrombocytopenia. Definite HIT was defined as an ICD-9-CM code for thrombocytopenia, together with discontinuation of heparin and initiation of treatment with argatroban. A definite complication was defined as HIT or evidence of major bleeding coupled with discontinuation of heparin. Finally, we evaluated all-cause in-hospital mortality and total hospital costs.

Statistical Analysis

We computed summary statistics using frequencies and percents for categorical variables, and means, medians, and standard deviations and interquartile range for continuous variables. Associations of prophylaxis type with patient and hospital characteristics and outcomes were assessed using chi-square tests or Fisher's exact test for categorical variables, and z-tests or Wilcoxon tests for continuous variables.

We developed a propensity model for treatment with UFH as the outcome; the model included patient characteristics, early treatments, comorbidities, risk factors for VTE, physician specialty, and selected interaction terms. We then developed a series of multivariable models to evaluate the impact of heparin choice on the risk of VTE, complications of treatment, mortality, and total cost. Generalized estimating equation models with a logit link were used to assess the association between the choice of heparin and the risk of VTE, and of complications and mortality, while adjusting for the effects of within-hospital correlation; identity link models were used for analyses of cost. Costs were trimmed at 3 standard deviations above the mean, and natural log-transformed values were modeled due to extreme positive skew.

Unadjusted and covariate-adjusted models were evaluated with and without adjustments for propensity score. In addition, since the hospital was the single strongest predictor of treatment, we developed grouped treatment models, in which a patient's actual treatment was replaced by a probability equal to the proportion of prophylaxed patients receiving UFH at that hospital. This adaptation of instrumental variable analysis uses the hospital as the instrument, and attempts to assess whether patients treated at a hospital which uses UFH more frequently have outcomes that differ from those of patients treated at hospitals which use LMWH more frequently, while adjusting for other patient, physician, and hospital variables. By relying on treatment at the hospital level, this method reduces the opportunity for selection bias at the patient level.

Finally, in order to exclude the possibility that our surrogate bleeding outcome was due to transfusion practices at hospitals that use a particular form of heparin, we compared the hospital rates of transfusion of 2 or more units of packed red cells to the hospital rates of prophylaxis with UFH in a larger dataset of the same hospitals. This set included patients with congestive heart failure, stroke, pneumonia, and urinary tract infection who did not receive daily prophylaxis, as well as patients admitted for chronic obstructive pulmonary disease (COPD) or acute myocardial infarction, and patients who received either warfarin or a treatment dose of heparin in the first 2 hospital days. We also compared the transfusion rates at hospitals that used unfractionated heparin in $\geq 80\%$ of patients to hospitals that used LMWH in $\geq 80\%$. All analyses were performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Our final sample included 32,104 patients who received prophylaxis at 333 hospitals (see Supporting Information, e-Figure, in the online version of this article). Patient characteristics appear in Table 1. Most patients (66%) were over age 65; 59% were female and 61% were white. The most common primary diagnoses were pneumonia (40%) and congestive heart failure (25%). Additional risk factors for thromboembolism included cancer (13%), paralysis (8%), or diabetes (35%). Most patients' attending physicians were either internists (61%) or family practitioners (14%). Almost half of the patients were cared for at hospitals in the South (46%).

Fifty-five percent of patients received LMWH and the remainder received UFH; 1274 (4%) patients switched type of heparin during their stay. The proportion of patients receiving LMWH at an individual hospital varied from 0% to 100% with a u-shaped distribution, with almost one-third of hospitals prescribing one treatment or the other exclusively (Figure 1). Similarly, the proportion of an individual physician's patients who received prophylaxis with UFH (vs LMWH)

varied from 0% to 100% (Figure 1), with 51% prescribing LMWH exclusively and 31% prescribing UFH exclusively. Compared to patients who received UFH, patients receiving LMWH were older and were more likely to be white, female, and to have pneumonia. By far the biggest difference between the groups was the hospitals at which they received their care (see Supporting Information, e-Table, in the online version of this article). Patients receiving LMWH were much more likely to be from smaller, rural, non-teaching hospitals in the South or the West. There were also numerous small differences in comorbidities and individual VTE risk factors between the 2 groups. The only large difference was that patients with a secondary diagnosis of renal failure (for which LMWH is not US Food and Drug Administration [FDA] approved) were almost twice as likely to receive UFH.

We identified 163 (0.51%) episodes of VTE (Table 2). Compared to patients receiving UFH, those receiving standard LMWH had similar unadjusted rates of VTE (0.53% vs 0.48%; $P = 0.54$), major bleeding (0.77% vs 0.76%; $P = 0.88$), thrombocytopenia (1.9% vs 2.0%; $P = 0.48$), definite HIT ($n = 1$ vs $n = 3$; $P = 0.34$), and mortality (2.8% vs 3.1%; $P = 0.07$). Definite complications of prophylaxis (HIT or major bleed combined with the discontinuation of heparin) were more common among patients receiving UFH (0.2% vs 0.1%; $P = 0.022$). Patients treated with UFH had longer unadjusted lengths of stay ($P < 0.0001$) and higher unadjusted costs ($P < 0.0001$).

A propensity model for UFH treatment based upon patient characteristics and treatments was not strongly predictive of treatment ($c = 0.58$) and propensity matching failed to balance many of the patient characteristics. However, hospital alone, ignoring patient characteristics was strongly predictive ($c = 0.91$) of treatment.

In a model adjusting only for clustering within hospitals, patients treated with UFH had an odds ratio (OR) for VTE of 1.08 (95% confidence interval [CI] 0.79 to 1.49) compared to patients receiving LMWH (Figure 2). Adjustment for propensity for UFH and other covariates attenuated the effect of LMWH (OR 1.04, 95% CI 0.76 to 1.43). When individual patients were assigned a probability of treatment with UFH equal to the hospital rate where they received care, UFH use was associated with a nonsignificant change in the odds of VTE (OR 1.14, 95% CI 0.72 to 1.81).

Adjusted for clustering within hospital only, patients treated with UFH had an odds ratio for major bleed of 1.38 (95% CI 1.00 to 1.91) compared to patients receiving LMWH (Figure 3). Adjustment for propensity for UFH and other covariates gave similar results (OR 1.34, 95% CI 0.97 to 1.84). When individual patients were assigned a probability of treatment with UFH equal to the hospital rate where they received care, UFH treatment was associated with a nonsignificant increase in the odds of major bleed (OR 1.64,

TABLE 1. Characteristics of Patients Receiving UFH and LMWH

	Total 32,104 (100) N (%)	UFH 14,591 (45.4) N (%)	LMWH 17,513 (54.6) N (%)	P
Demographics				
Age				0.0002
18–49	4,061 (12.7)	1,950 (13.4)	2,111 (12.1)	
50–64	6,962 (21.7)	3,225 (22.1)	3,737 (21.3)	
65–79	10,909 (34.0)	4,921 (33.7)	5,988 (34.2)	
80+	10,172 (31.7)	4,495 (30.8)	5,677 (32.4)	
Sex				0.0071
Male	13,234 (41.2)	6,133 (42.0)	7,101 (40.5)	
Female	18,870 (58.8)	8,458 (58.0)	10,412 (59.5)	
Race/ethnicity				<0.0001
White	19,489 (60.7)	8,063 (55.3)	11,426 (65.2)	
Black	7,429 (23.1)	4,101 (28.1)	3,328 (19.0)	
Hispanic	1,304 (4.1)	591 (4.1)	713 (4.1)	
Other	3,882 (12.1)	1,836 (12.6)	2,046 (11.7)	
Primary diagnosis				<0.0001
Pneumonia	12,768 (39.8)	5,354 (36.7)	7,414 (42.3)	
Sepsis*	1,217 (3.8)	562 (3.9)	655 (3.7)	
Respiratory failure*	2,017 (6.3)	814 (5.6)	1,203 (6.9)	
Heart failure	8,157 (25.4)	3,825 (26.2)	4,332 (24.7)	
Stroke	4,416 (13.8)	2,295 (15.7)	2,121 (12.1)	
Urinary tract infection	3,529 (11.0)	1,741 (11.9)	1,788 (10.2)	
Attending specialty				<0.0001
Internist	19,511 (60.8)	8,945 (61.3)	10,566 (60.3)	
General practice/Family medicine	4,326 (13.5)	1,964 (13.5)	2,362 (13.5)	
Cardiologist	1,606 (5.0)	730 (5.0)	876 (5.0)	
Pulmonologist	2,179 (6.8)	854 (5.9)	1,325 (7.6)	
Nephrology	583 (1.8)	380 (2.6)	203 (1.2)	
Critical care/Intensivist	150 (0.5)	93 (0.6)	57 (0.3)	
Other	3,749 (11.7)	1,625 (11.1)	2,124 (12.1)	
Insurance				<0.0001
Medicare traditional	20,281 (63.2)	8,929 (61.2)	11,352 (64.8)	
Medicare managed care	1,737 (5.4)	826 (5.7)	911 (5.2)	
Medicaid	2,629 (8.2)	1,401 (9.6)	1,228 (7.0)	
Private	5,967 (18.6)	2,830 (19.4)	3,137 (17.9)	
Self-pay/uninsured/other	1,490 (4.6)	605 (4.1)	885 (5.1)	
Risk factors for VTE				
Admit from skilled nursing facility	476 (1.5)	277 (1.9)	199 (1.1)	<0.0001
Paralysis	2,608 (8.1)	1,317 (9.0)	1,291 (7.4)	<0.0001
Restraints	417 (1.3)	147 (1.0)	270 (1.5)	<0.0001
Decubitus ulcer	1,190 (3.7)	631 (4.3)	559 (3.2)	<0.0001
Cancer	4,154 (12.9)	1,858 (12.7)	2,296 (13.1)	0.3171
Chemotherapy	86 (0.3)	41 (0.3)	45 (0.3)	0.6781
Prior venous thromboembolism	494 (1.5)	202 (1.4)	292 (1.7)	0.0403
Pregnancy	1 (0)	1 (0)	0 (0)	0.2733
Estrogens	438 (1.4)	143 (1.0)	295 (1.7)	<0.0001
Estrogen modulators	246 (0.8)	80 (0.5)	166 (0.9)	<0.0001
Congestive heart failure	3,107 (9.7)	1,438 (9.9)	1,669 (9.5)	0.3263
Respiratory failure	2,210 (6.9)	1,037 (7.1)	1,173 (6.7)	0.1493
Inflammatory bowel disease	108 (0.3)	41 (0.3)	67 (0.4)	0.1176
Nephrotic syndrome	92 (0.3)	50 (0.3)	42 (0.2)	0.0860
Myeloproliferative disorder	198 (0.6)	68 (0.5)	130 (0.7)	0.0016
Obesity	2,973 (9.3)	1,211 (8.3)	1,762 (10.1)	<0.0001
Smoking	4,476 (13.9)	1,887 (12.9)	2,589 (14.8)	<0.0001
Varicose veins	19 (0.1)	6 (0)	13 (0.1)	0.2245
Central line	1,070 (3.3)	502 (3.4)	568 (3.2)	0.3271
Inherited or acquired thrombophilia	16 (0)	9 (0.1)	7 (0)	0.3855
Diabetes	11,136 (34.7)	5,157 (35.3)	5,979 (34.1)	0.0241
Procedures associated with VTE or bleed				
Mechanical ventilation	2,282 (7.1)	1,111 (7.6)	1,171 (6.7)	0.0013
Urinary catheter	4,496 (14.0)	1,545 (10.6)	2,951 (16.9)	<0.0001
Aspirin	12,865 (40.1)	6,101 (41.8)	6,764 (38.6)	<0.0001
Clopidogrel	4,575 (14.3)	2,087 (14.3)	2,488 (14.2)	0.8050
Non-steroidal anti-inflammatory drugs	2,147 (6.7)	867 (5.9)	1,280 (7.3)	<0.0001

(Continued)

TABLE 1. (Continued)

	Total 32,104 (100) N (%)	UFH 14,591 (45.4) N (%)	LMWH 17,513 (54.6) N (%)	P
Steroids	7,938 (24.7)	3,136 (21.5)	4,802 (27.4)	<0.0001
Statins	7,376 (23.0)	3,462 (23.7)	3,914 (22.3)	0.0035
Comorbidities				
AIDS	124 (0.4)	73 (0.5)	51 (0.3)	0.0026
Alcohol abuse	1,048 (3.3)	523 (3.6)	525 (3.0)	0.0032
Deficiency anemia	7,010 (21.8)	3,228 (22.1)	3,782 (21.6)	0.2543
Rheumatoid arthritis/collagen vas	967 (3.0)	426 (2.9)	541 (3.1)	0.3762
Chronic blood loss anemia	177 (0.6)	79 (0.5)	98 (0.6)	0.8269
Chronic pulmonary disease	12,418 (38.7)	5,314 (36.4)	7,104 (40.6)	<0.0001
Depression	3,334 (10.4)	1,433 (9.8)	1,901 (10.9)	0.0025
Drug abuse	694 (2.2)	412 (2.8)	282 (1.6)	<0.0001
Hypertension	16,979 (52.9)	7,658 (52.5)	9,321 (53.2)	0.1866
Hypothyroidism	4,016 (12.5)	1,716 (11.8)	2,300 (13.1)	0.0002
Liver disease	453 (1.4)	227 (1.6)	226 (1.3)	0.0448
Other neurological disorders	4,682 (14.6)	2,202 (15.1)	2,480 (14.2)	0.0187
Peripheral vascular disease	2,134 (6.6)	980 (6.7)	1,154 (6.6)	0.6490
Psychoses	1,295 (4.0)	574 (3.9)	721 (4.1)	0.4066
Pulmonary circulation disease	1,034 (3.2)	442 (3.0)	592 (3.4)	0.0760
Renal failure	2,794 (8.7)	1,636 (11.2)	1,158 (6.6)	0.0000
Peptic ulcer disease with bleeding	563 (1.8)	232 (1.6)	331 (1.9)	0.0414
Valvular disease	2,079 (6.5)	899 (6.2)	1,180 (6.7)	0.0366
Weight loss	1,231 (3.8)	556 (3.8)	675 (3.9)	0.8391
Other prophylaxis				
Intermittent pneumatic compression	1,003 (3.1)	456 (3.1)	547 (3.1)	0.9926
Mechanical prophylaxis	1,281 (4.0)	524 (3.6)	757 (4.3)	0.0009

Abbreviations: AIDS, acquired immune deficiency syndrome; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism. *With secondary diagnosis of pneumonia.

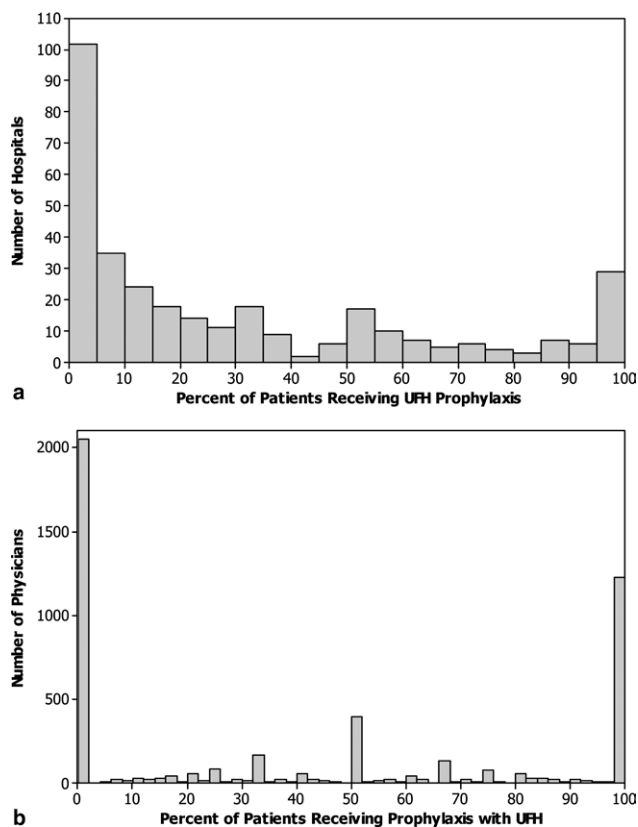


FIG. 1. (a) Distribution of 333 hospitals using various proportions of unfractionated heparin (UFH) prophylaxis. (b) Distribution of 4898 physicians using various proportions of UFH prophylaxis. Includes only physicians contributing at least 2 patients.

95% CI 0.50 to 5.33). When we compared the rate of transfusion across hospitals, including 576,231 additional patients who were excluded from the original analyses because they did not receive daily prophylaxis or had a diagnosis of myocardial infarction or COPD, there was a slight negative correlation between transfusion rates and use of UFH (Spearman Correlation Coefficient -0.03 ; $P = 0.61$). Hospitals that used primarily UFH had a transfusion rate of 0.60% versus 0.76% at hospitals using primarily LMWH ($P = 0.54$), indicating that the increased risk of major bleeding associated with UFH was not confounded by local transfusion practices.

Adjusted for clustering only, patients treated with UFH had an odds ratio for definite complication of 2.35 (95% CI 1.17 to 4.72) compared to those treated with LMWH. Adjustment for propensity and covariates accentuated the association (OR 2.84, 95% CI 1.43 to 5.66). When assigned a probability of treatment with UFH equal to the hospital rate where they received care, UFH treatment was associated with an increase in the risk of definite complication (OR 2.79, 95% CI 1.00 to 7.74).

Adjusted for clustering only, patients treated with UFH had higher costs than those treated with LMWH (cost ratio 1.07, 95% CI 1.05 to 1.09). Adjustment for propensity for UFH and other covariates attenuated the association (cost ratio 1.02, 95% CI 1.00 to 1.03). Finally, when individual patients were assigned

TABLE 2. Unadjusted Outcomes for Patients Receiving Prophylaxis With UFH and LMWH

	Total 32,104 (100) n (%)	UFH 14,591 (45.4) n (%)	LMWH 17,513 (54.6) n (%)	P
Venous thromboembolism	163 (0.5)	78 (0.5)	85 (0.5)	0.54
Heparin-induced thrombocytopenia	4 (0)	3 (0)	1 (0)	0.34*
Any major bleeding	246 (0.8)	113 (0.8)	133 (0.8)	0.88
Transfusion with ≥2 units of packed red blood cells	218 (0.7)	97 (0.7)	121 (0.7)	0.78
Intracranial hemorrhage	30 (0.1)	17 (0.1)	13 (0.1)	0.22
Complication resulting in stopping heparin	44 (0.1)	28 (0.2)	16 (0.1)	0.02
In-hospital mortality	944 (2.9)	456 (3.1)	488 (2.8)	0.07
LOS in days; mean (SD)	6.2 (5.9)	6.4 (6.2)	6.0 (5.6)	<0.001 [†]
Median (IQR)	5 (3-7)	5 (3-7)	5 (3-7)	
Cost in USD; median (IQR)	5873 (4171-8982)	6007 (4177-9456)	5774 (4165-8660)	<0.001 [†]

Abbreviations: IQR, interquartile range; LMWH, low-molecular-weight heparin; LOS, length of stay; SD, standard deviation; UFH, unfractionated heparin; USD, US dollars. *Fisher's exact test; [†]Kruskal-Wallis analysis of variance (ANOVA).

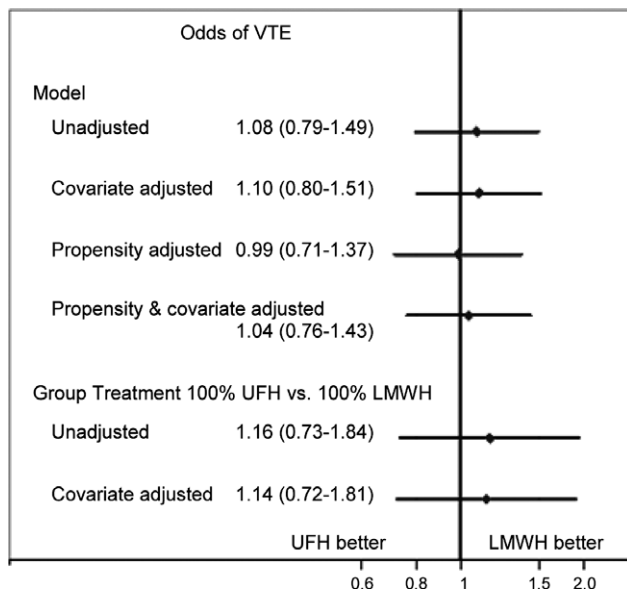


FIG. 2. Odds ratio for venous thromboembolism (VTE) for unfractionated heparin (UFH) relative to low-molecular-weight heparin (LMWH) by model. Values less than 1.0 favor UFH.

a probability of initial treatment with UFH equal to the hospital rate where they received care, treatment with UFH was associated with a nonsignificant change in the relative cost (cost ratio 0.97, 95% CI 0.90 to 1.05).

DISCUSSION

In this retrospective cohort study, we found that low-molecular-weight heparin and unfractionated heparin were associated with similar rates of VTE in moderate-to-high risk medical patients. However, unfractionated heparin was associated with a small, but higher risk of complications, even after adjustment. There were no statistical differences in rates of heparin-induced thrombocytopenia, but this complication was exceedingly rare. Finally, overall costs associated with both treatments were similar.

A number of industry-funded studies have compared LMWH to UFH in randomized clinical trials. These

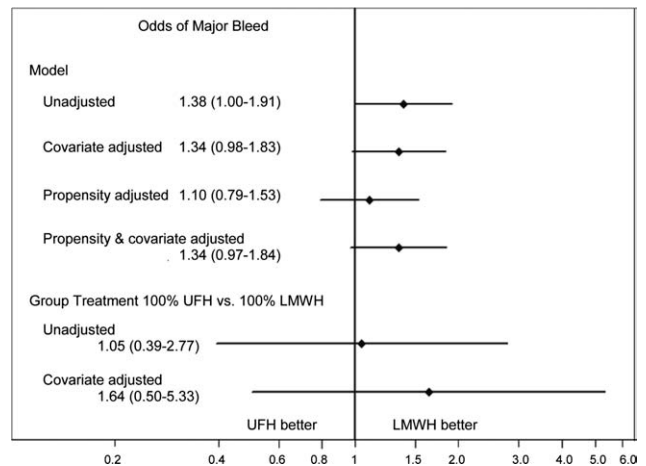


FIG. 3. Odds ratio for bleeding for unfractionated heparin (UFH) relative to low-molecular-weight heparin (LMWH) by model. Values less than 1.0 favor UFH.

trials have generally been small and used endpoints of uncertain significance, such as asymptomatic deep vein thrombosis assessed by ultrasound. At least 3 meta-analyses of these trials have been published. Each used different inclusion criteria. The only one to find an efficacy benefit to LMWH over UFH was heavily influenced by the inclusion of a number of studies of stroke patients.³ In that study, LMWH reduced VTE by approximately one-third relative to UFH. The other 2 analyses found smaller reductions in DVT and pulmonary embolism (PE), and these results were not statistically significant.^{5,8} Similarly, 1 analysis⁵ found a reduction in major bleeding events with LMWH versus UFH, whereas the other 2 studies found smaller reductions which were not statistically significant. The assessment of major bleeding is further complicated by differences in the definition of major bleeding across studies. Using a standard definition of 2 units of packed red blood cells transfused in 1 day to denote major bleeding, we found an associated reduction in bleeding with LMWH that was similar to that observed in the meta-analyses. Moreover, patients receiving UFH were twice as likely to have a

complication that resulted in stopping the prophylaxis, although these complications were overall quite rare. Lastly, there are no cost comparisons based on randomized trials. Several comparisons based on modeling have favored LMWH. One assumed that 3% of patients receiving UFH would develop HIT;¹³ something we did not observe. At least 3 additional analyses,^{14–16} all funded by the manufacturer of enoxaparin, assumed that LMWH was both more effective and safer than UFH. We found that adjusted costs were similar or slightly lower with UFH than LMWH.

Our study has a number of limitations. First, its observational design makes it vulnerable to selection bias. We attempted to overcome this with rigorous multivariable adjustment, including the propensity for treatment and by using an adaptation of the instrumental variable approach. This method is of particular interest because individual hospitals were strongly predictive of choice of heparin. Still, we cannot exclude the possibility of residual confounding, especially if other outcomes, such as transfusion decisions, were also tied to specific hospital practices. Second, our study used administrative data, and therefore we could not directly adjust for certain differences which may exist between patients who received LMWH and those who received UFH. However, we did adjust for many classic risk factors for VTE. More importantly, it seems that the chance of being treated with a particular form of heparin depends more on the hospital where one receives care than on any combination of patient characteristics. Thus, apart from renal failure, for which we adjusted, it seems unlikely that there were major differences in unmeasured physiological confounders. Third, we limited our analysis to patients who received standard dosing of either type of heparin. We did this to bolster the validity of our findings, but they may not apply to unconventional dosing often observed in clinical practice. Fourth, we measured only outcomes that occurred in the hospital or that prompted a return to the hospital. VTEs which were diagnosed and treated in ambulatory care were not included. While this may have led us to underestimate the true risk of VTE, we have little reason to believe that the choice of whether to admit a patient with VTE is influenced by the original choice of VTE prophylaxis. Finally, our study was conducted before the introduction of generic LMWH, which would be expected to reduce costs associated with LMWH prophylaxis.

VTE prophylaxis for medical patients has emerged as a major focus for quality improvement initiatives. As a result, a significant proportion of general medical patients receive some form of chemoprophylaxis during their hospital stay. Small differences in efficacy or safety of different forms of prophylaxis multiplied by millions of admissions each year can have profound effects on the health of hospitalized patients. Similarly, differences in cost could also have a substantial impact on the healthcare system. We found no difference in efficacy or cost, but treatment with LMWH was less

likely to be associated with subsequent transfusion of 2 or more units of packed red blood cells, a surrogate marker for bleeding. In addition, LMWH is more convenient since it can be dosed once daily, and for that reason may be more acceptable to patients. For these reasons, LMWH may be the drug of choice for inpatient prophylaxis of general medical patients. In situations where the cost of the medication itself is important, UFH represents an equally effective alternative.

Acknowledgements

All authors have contributed sufficiently to this study and have provided written permission to be named in the manuscript. No other persons have made substantial contributions to this manuscript. Michael B. Rothberg is the guarantor of the entire manuscript. Disclosures: This study was supported by a Clinical Scientist Development Award from the Doris Duke Charitable Foundation. The funding source had no role in the study design, analysis, or interpretation of the data. Dr Rothberg served for 1 day as a consultant to Novartis Pharma about an influenza vaccine model. Sandoz, a division of Novartis, was recently granted approval to manufacture a generic form of low-molecular-weight heparin. None of the other authors have any conflicts of interest.

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