ORIGINAL RESEARCH ARTICLE

Real-World Comparative Effectiveness and Cost Comparison of Thromboprophylactic Use of Enoxaparin versus Unfractionated Heparin in 376,858 Medically Ill Hospitalized US Patients

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Abstract

Background Venous thromboembolism (VTE) is a serious complication in medically ill inpatients. Enoxaparin or unfractionated heparin (UFH) thromboprophylaxis has been shown to reduce VTE in clinical trials; however, comparative effectiveness and differences in hospital costs are unknown in US hospital practice.

Objective This study compared clinical and economic outcomes between enoxaparin and UFH thromboprophylaxis in medically ill inpatients.

Methods A retrospective cohort study was conducted using the Premier Healthcare Database between 1 January 2010 and 30 September 2016. Inpatients aged ≥ 18 years with a ≥ 6-day hospital stay for serious medical conditions were included. Two patient groups receiving thromboprophylaxis were identified during hospitalization: one receiving enoxaparin and other receiving UFH. Regression models were constructed to compare VTE events, in-hospital mortality, pulmonary embolism (PE)-related mortality, major bleeding, and total hospital costs during both the index hospitalization and the 90-day readmission period between the two groups.

Results A total of 242,474 and 134,384 inpatients received enoxaparin or UFH for thromboprophylaxis, respectively. Compared with UFH prophylaxis, enoxaparin was significantly associated with 15%, 9%, 33%, and 41% reduced odds of VTE, in-hospital mortality, PE-related mortality, and major bleeding, respectively, during index hospitalization, and 10% and 19% reduced odds of VTE and bleeding, respectively, during the readmission period. Mean total hospital costs were significantly lower in patients receiving enoxaparin prophylaxis than in those given UFH.

Conclusions Thromboprophylaxis with enoxaparin was associated with significantly reduced in-hospital VTE events, death, and major bleeding and lower hospital costs compared with UFH in hospitalized medically ill patients.

Key Points

Thromboprophylaxis is recommended for medical inpatients at risk of venous thromboembolism.

Enoxaparin versus unfractionated heparin prophylaxis was associated with reduced in-hospital venous thromboembolism, death, and bleeding.

Prophylaxis with enoxaparin compared with unfractionated heparin was associated with lower hospital costs.

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1 Introduction

Venous thromboembolism (VTE), manifesting as deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a serious medical condition causing significant morbidity and mortality. It has been estimated that approximately 2014US$12,000–15,000 are required to treat one incident acute VTE event, and approximately 2014US$18,000–23,000 to treat subsequent complications, resulting in an overall economic burden of 2014US$7–10 billion annually in the USA [1]. Hospitalization for a serious medical condition is a transiently acquired risk factor associated with increased risk of VTE [2]. Medically ill inpatients, including those hospitalized for pulmonary diseases, circulatory disorders, infections, or cancer, often have prolonged hospital stays with periods of immobility and are found to have an at least tenfold increased risk of VTE [3–5]. An estimated 10–20% of these patients

develop VTEs in the absence of thromboprophylaxis [6, 7]. Thus, the American College of Chest Physicians and American Society of Hematology have recommended pharmacologic thromboprophylaxis for all hospitalized patients at risk of VTE [8, 9].

Low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) are the most commonly used anticoagulants for thromboprophylaxis in medically ill hospitalized patients. Meta-analyses have demonstrated that thromboprophylaxis with LMWH or UFH reduced the incidence of DVT by up to 67% and of PE by up to 74% [10–12]. In addition, clinical trials have reported that thromboprophylaxis with enoxaparin, the most commonly prescribed LMWH, was cost effective and significantly reduced VTE events in medically ill inpatients without increasing adverse events compared with UFH [13–17]. However, differences in clinical outcomes and hospital costs between them is largely unknown in current hospital practice in the USA. This study assessed the use of enoxaparin and UFH among hospitalized medically ill patients. Specifically, it sought to compare clinical and economic outcomes between medically ill patients who received either enoxaparin or UFH for VTE prophylaxis during their hospitalization.

2 Methods

2.1 Study Design and Data Source

A retrospective cohort study was conducted using the Premier Healthcare Database (PHD). The PHD is a large hospital-based, service-level, all-payer database representing approximately 25% of all annual admissions from diverse non-profit, non-governmental, community and teaching hospitals, and health systems from rural and urban areas in the USA [18]. At the time of this study, more than 850 hospitals contributed data to the PHD. Through a unique masked identifier, patients in the PHD can be tracked across inpatient and outpatient encounters to the same hospital system. Data extracted from standard hospital discharge files include patient demographics and disease status, admission and discharge diagnoses, information on date-stamped billed items at the departmental level for medications, services, procedures, laboratory tests, and diagnostic and therapeutic services, microbiology tests, and patient disposition and discharge health status. Information on medication utilization is available by day of patient hospital stay and includes dose, quantity, strength, and cost per dose. Data used for this study were de-identified, Health Insurance Portability and Accountability Act compliant, and considered exempt from institutional review board oversight as per 45 CFR 46.101(b)(4).

2.2 Study Population

Adult patients aged ≥18 years with an inpatient admission between 1 January 2010 and 30 September 2016, a hospital stay of at least 6 days, and a primary or secondary admission or discharge *International Classification of Diseases, Ninth Revision* (ICD)-9 and *Tenth Revision, Clinical Modification* (-10-CM) code for circulatory disorders (ICD-9-CM: 390.xx–459.xx; ICD-10-CM: I00.xxx–I99.xxx), respiratory conditions (ICD-9-CM: 460.xx–519.xx; ICD-10-CM: J00.xxx–J99.xxx), infectious diseases (ICD-9-CM: 001.xx–139.xx, 680.xx–686.xx, 730.xx, 996.xx–999.xx; ICD-10-CM: A00.xxx–B99.xxx, J02.xxx–J03.xxx, K11.xxx–K65.xxx, L00.xxx–L99.xxx, M46.xxx, M86.xxx–M90.xxx, T80.xxx–T88.xxx), or neoplasms (ICD-9-CM: 140.xx–239.xx; ICD-10-CM: C00.xxx–D49.xxx) were identified (index hospitalization period). To minimize the effect of bias or confounding, patients were excluded if they met certain criteria during the index hospitalization and 90 days preceding the index hospitalization admission (pre-index hospitalization period). The primary exclusion criteria included patients with VTE diagnoses and/or therapeutic use of anticoagulants during the pre-index hospitalization period and within the first 2 days of index hospitalization admission. Patients with receipt of mechanical methods of VTE prophylaxis, receipt of vitamin K antagonists, diagnoses with thrombophilic conditions or hemorrhagic disorders, active peptic ulcer, or any surgery during the pre-index and index hospitalization periods were excluded. Patients included in the final assessment received VTE prophylaxis with either enoxaparin or UFH. Patients who received any combination of enoxaparin and UFH or received another anticoagulant (including fondaparinux, dalteparin, and rivaroxaban) along with enoxaparin or UFH were excluded. Patients were followed for up to 90 days after index hospitalization discharge to capture study outcomes among those who were readmitted to the same hospital (readmission period).

2.3 Study Measures

The primary clinical outcome was the occurrence of VTE during index hospitalization and readmission periods. A VTE event was defined using either primary or secondary admission or discharge ICD-9/10-CM diagnosis codes for DVT (ICD-9-CM: 451.xx–453.xx; ICD-10-CM: I80.xxx–I82.xxx) and/or PE (ICD-9-CM: 415.1x; ICD-10-CM: I26.9x and T80.xxxx–T82.xxxx). Secondary clinical outcomes included in-hospital mortality and mortality related to PE during index hospitalization and readmission periods. Economic outcomes included total hospitalization costs during index hospitalization and readmission periods and pharmacologic prophylaxis costs during the index hospitalization period. Pharmacologic prophylaxis costs included total costs

for all prophylactic doses of enoxaparin and UFH and were determined from the hospitals' charge master data.

Major bleeding events and heparin-induced thrombocytopenia (HIT) during the index hospitalization and readmission periods were identified. A major bleeding event was defined by the presence of a primary or secondary admission or discharge ICD-9/10-CM diagnosis code for serious bleeding (ICD-9-CM: 430, 431, 432.x, 459.0, 578.x, 786.3x; ICD-10-CM: I60.9–I62.9, R58, K92.0, K92.2, R04.x, D75.82). HIT was defined by the presence of a primary or secondary admission or discharge ICD-9-CM diagnosis code of 289.84 or ICD-10-CM diagnosis code of D75.82.

The study exposure was VTE prophylaxis with either enoxaparin or UFH. Patients were categorized based on receipt of at least one prophylactic dose (enoxaparin ≤ 40 mg/day; UFH ≤ 15,000 IU/day) during the index hospitalization as determined from the hospitals' charge master data. Patients who received VTE prophylactic doses of both enoxaparin and UFH were not included.

Several variables, including patient demographic, visit, clinical, and hospital characteristics, that might confound the relationship between enoxaparin prophylaxis and study outcomes were assessed during index hospitalization and included as covariates. Patient demographics included age, sex, race, and payer type. Visit characteristics included admission type and source, discharge disposition, ICU admissions, and hospital length of stay. Comorbidities identified by the presence of ICD-9/10 diagnoses codes during the index hospitalization included congestive heart failure (ICD-9-CM: 428–428.9x; ICD-10-CM: I50.1, I50.20–I50.23, I50.33, I50.40–I50.43, I50.9), myocardial infarction (ICD-9-CM: 410–410.9x, 412–412.9x; ICD-10-CM: I21.x, I22.x, I25.2, I23.x), chronic obstructive pulmonary disease (ICD-9-CM: 490–496.9x, 500–505.9x, 506.4x; ICD-10-CM: J40, J41.x, J42, J43.9, J44.x, J45.2x, J45.90x, J45.99x, J47.1, J47.9, J60, J61, J62.8, J63.x, J66.x, J64, J67.x, J68.4), fracture of lower limb (ICD-9-CM: 820.x; ICD-10-CM: S82.x), inflammatory bowel disease (ICD-9-CM: 555–556.x; ICD-10-CM: K50–K51.xxx), intubation (ICD-9-Procedure Classification System (PCS): I96.0x–96.5x, 96.6, 96.7x; ICD-10-PCS: 09Hxxxx, 099xxxx, 0BHxxxx, 0B9xxxx, 0D9xxxx, 0T7xxxx, 0UHxxxx, 0WHxxxx, 0YQxxxx), malignant hypertension (ICD-9-CM: 401.0, 402–405.xx; ICD-10-CM: I10, I11–I13.xx, I15.x), myocardial infarction (ICD-9-CM: 410–410.9x, 412–412.9x; ICD-10-CM: I21.x, I22.x, I25.2, I23.x), nephrotic syndrome (ICD-9-CM: 581. xx; ICD-10-CM: N04.x), and obesity (ICD-9-CM: 278; ICD-10-CM: E66). In addition, 3M™ All Patient Refined™ Diagnosis-Related Group (APR™-DRG) Severity of Illness (APR-SOI) [19], and the Deyo modification of the Charlson Comorbidity Index (CCI) [20] were used to assess health status. The APR-SOI (minor, moderate, major, or extreme) was computed at the time of hospital discharge and accounts

for age, procedures, and clinical severity of primary diagnosis and all secondary diagnoses assigned in the course of index hospitalization [19]. Hospital characteristics included teaching status, bed size, geographical region, and population served.

2.4 Statistical Analysis

Descriptive statistics were presented using mean ± standard deviation (SD) for continuous variables and using frequencies and proportions for categorical variables. Bivariate analyses were conducted to assess differences in patient demographics and visit, clinical, and hospital characteristics between enoxaparin and UFH prophylaxis groups using Student's t-test or the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Normality of the data was assessed by histogram and the Kolmogorov–Smirnov test to determine the appropriate tests to apply for statistical significance. Multivariable logistic regression models were conducted to estimate the odds of VTE events, in-hospital mortality, PE-related mortality, and major bleeding between enoxaparin and UFH prophylaxis groups during the index hospitalization and readmission periods. Economic outcomes, including total hospitalization costs and pharmacologic prophylaxis costs during the index hospitalization period, and total hospitalization costs during the readmission period, were reported using unadjusted mean ± SD. Outliers were assessed and those < 1st percentile and > 99th percentile were excluded. Generalized linear models with gamma link function were constructed to estimate adjusted costs for each study group and presented using adjusted means and confidence intervals (CIs). Patients with missing cost data were excluded from the study. All regression models were assessed for fitness and convergence of algorithm. Regression diagnostics were conducted to assess multicollinearity between variables and did not warrant deletion of any variables. A $p < 0.05$ was used for statistically significant inferences. Data management and analyses were performed using SAS v. 9.4 (SAS Institute Inc., Cary, NC, USA).

3 Results

A total of 376,858 medically ill inpatients met the study criteria, with 64% (242,474) receiving VTE prophylaxis with enoxaparin and 36% (134,384) receiving UFH during index hospitalization. Table 1 presents patient demographics and visit, clinical, and hospital characteristics for the two VTE prophylactic groups. Statistically significant differences in all variables were observed between the two study groups ($p < 0.05$). Compared with medically ill inpatients with UFH prophylaxis, those with enoxaparin prophylaxis were younger (mean age of 65 ± 17 vs. 67 ± 16 years), more

likely to be female (55 vs. 50%), predominantly White (74 vs. 68%), and less likely to be Medicare beneficiaries (61 vs. 65%) ($p < 0.0001$ for each).

A significantly higher proportion of patients in the enoxaparin group compared with the UFH group were admitted emergently (75 vs. 72%) from a non-healthcare facility (79 vs. 75%) and discharged to home (69 vs. 64%) ($p < 0.0001$ for each). The proportion of enoxaparin patients with extreme SOI (18 vs. 25%) and a CCI score of ≥ 2 (36 vs. 47%) was significantly lower than that of UFH inpatients ($p < 0.0001$ for each). Compared with the UFH group, a higher proportion of patients in enoxaparin group had a comorbid condition of chronic obstructive pulmonary disease (47 vs. 38%) and malignant hypertension (10 vs. 9%) ($p < 0.0001$ for each). Moreover, a greater proportion of enoxaparin patients compared with UFH patients were treated in non-teaching hospitals (62 vs. 44%) of smaller bed capacity (36 vs. 31%) located in the southern USA (54 vs. 34%) that served rural populations (13 vs. 8%) ($p < 0.0001$ for each).

3.1 Comparative Effectiveness

Table 2 presents the clinical outcomes during the index hospitalization and readmission periods for the enoxaparin and UFH prophylaxis groups. During index hospitalization, VTE event, in-hospital mortality, and PE-related mortality rates were 0.47%, 3.58%, and 0.03%, respectively, for the enoxaparin group and 0.76%, 5.47%, and 0.08%, respectively, for the UFH group. Multivariable regression analyses revealed that enoxaparin prophylaxis was significantly associated with a lower odds of 15% for VTE events (odds ratio [OR] 0.85; $p = 0.001$), 9% for in-hospital mortality (OR 0.91; $p < 0.0001$), and 33% for PE-related mortality (OR 0.67; $p = 0.015$) than UFH prophylaxis during the index hospitalization period. A total of 105,836 (44%) in the enoxaparin group and 57,763 (43%) in the UFH group were readmitted for any cause within 90 days after discharge from index hospitalization. Among readmitted patients, VTE event, in-hospital mortality, and PE-related mortality rates were 2.71%, 4.32%, and 0.18% for the enoxaparin group and 3.15%, 4.90%, and 0.15%, respectively, for the UFH group. Compared with UFH prophylaxis, enoxaparin prophylaxis was significantly associated with a 10% lower odds of a VTE (OR 0.90; $p = 0.0022$) and 8% higher odds of inpatient death (OR 1.08; $p = 0.008$) in readmitted inpatients. No statistically significant differences in PE-related mortality were observed.

3.2 Major Bleeding and Heparin-Induced Thrombocytopenia

During the index hospitalization, 5328 (2.2%) patients in the enoxaparin group and 6281 (4.7%) in the UFH group

were coded with a major bleeding event ($p < 0.0001$). During the readmission period, 3161 (3%) patients in the enoxaparin group and 2374 (4.1%) in the UFH group were similarly coded ($p < 0.0001$). The enoxaparin group had a 41% lower risk of bleeding during the index encounter visit (OR 0.59; 95% CI 0.57–0.62) and a 19% lower risk in the 90-day follow-up period (OR 0.81; 95% CI 0.77–0.86) than those treated with UFH. HIT was identified in 105 (0.04%) patients in the enoxaparin group and 172 (0.1%) patients in the UFH group ($p < 0.0001$) during the index hospitalization and 67 (0.06%) patients in the enoxaparin group and 96 (0.2%) patients in the UFH group ($p < 0.0001$) during the readmission period.

3.3 Economic Outcomes

Table 3 presents unadjusted and adjusted total hospitalization costs during index hospitalization and readmission periods and unadjusted and adjusted pharmacologic prophylaxis costs during the index hospitalization period. Compared with UFH prophylaxis, patients with enoxaparin prophylaxis had significantly lower adjusted mean total hospitalization costs during the index period (2014US\$15,665 [95% CI 15,386–15,907] vs. 17,092 [95% CI 16,887–17,320]; $p < 0.0001$) and during the readmission period (2014US\$5108 [95% CI 4707–5544] vs. 5455 [95% CI 5194–5921]; $p < 0.0001$). Higher adjusted mean pharmacologic prophylaxis costs during index hospitalization were noted for enoxaparin compared with UFH (2014US\$140 [95% CI 136–145] vs. 67 [95% CI 65–69]; $p < 0.0001$).

4 Discussion

A large hospital database was used to assess the real-world use of thromboprophylaxis with enoxaparin and UFH in hospitalized medically ill patients in the USA. Prophylaxis with enoxaparin versus UFH was associated with a statistically significant lower odds of VTE events, hospital deaths, deaths related to PE, and major bleeding during index hospitalization and of VTE events and major bleeding among patients readmitted within 90 days of index discharge. In addition, there was a lower adjusted mean hospitalization cost during index hospitalization and the readmission period for those in the enoxaparin versus UFH groups. Other studies have found inconsistent results, likely because of differences in study populations and designs.

Several randomized controlled trials comparing enoxaparin and UFH prophylaxis in non-surgical medical inpatients who were at risk of VTE found greater reductions in VTE events than observed in our study [14–17]. This may reflect the more homogenous populations of patients with

Table 1 Patient demographic, clinical, and hospital characteristics of medically ill patients on enoxaparin versus unfractionated heparin prophylaxis

Characteristics	Enoxaparin prophylaxis (N = 242,474)	Unfractionated heparin prophylaxis (N = 134,384)	p-Value
Patient demographic characteristics			
Age (years)	65 ± 17	67 ± 16	< 0.0001
Female sex	132,994 (55)	67,050 (50)	< 0.0001
Race			
White	179,776 (74)	91,357 (68)	< 0.0001
Black	29,059 (12)	19,114 (14)	
Other	32,642 (14)	23,551 (18)	
Unknown	997 (0.4)	362 (0.3)	
Payer type			
Private	47,395 (20)	25,653 (19)	< 0.0001
Medicaid	28,157 (12)	14,640 (11)	
Medicare	147,754 (61)	86,792 (65)	
Uninsured	15,631 (7)	5927 (4)	
Unknown	3537 (2)	1372 (1)	
Visit characteristics			
Admission source			
Non-healthcare facility of origin	192,579 (79)	100,534 (75)	< 0.0001
Transfer from acute care facility	20,245 (8)	17,243 (13)	
Transfer from long-term care facility	5991 (3)	4216 (3)	
Clinic/emergency room	15,125 (6)	7350 (6)	
Other/unknown	8534 (4)	5041 (4)	
Admission type			
Emergency	181,114 (75)	96,399 (72)	< 0.0001
Urgent	37,858 (16)	21,133 (16)	
Elective	21,567 (9)	15,611 (12)	
Trauma	786 (0.3)	629 (0.5)	
Discharge status			
Expired	8673 (4)	7350 (6)	< 0.0001
Home	166,515 (69)	86,070 (64)	
Transferred to another acute care	3849 (2)	2434 (2)	
Transferred to nursing or rehabilitation facility	59,602 (25)	36,178 (27)	
Other/unknown	3835 (2)	2352 (2)	
ICU admission stay	62,993 (26)	45,683 (34)	< 0.0001
Hospital length of stay (days)	8.7 ± 4.6	9.1 ± 5.9	< 0.0001
Clinical characteristics			
Severity of illness			< 0.0001
Minor	14,968 (6)	7439 (6)	
Moderate	73,587 (30)	32,914 (25)	
Major	109,374 (45)	60,781 (45)	
Extreme	44,545 (18)	33,250 (25)	
Charlson Comorbidity Index Score[a]			< 0.0001
0	34,326 (14)	15,447 (12)	
1–2	121,194 (50)	55,862 (42)	
≥ 2	86,954 (36)	63,075 (47)	
Congestive heart failure	58,488 (24)	42,726 (32)	< 0.0001
COPD	114,174 (47)	51,011 (38)	< 0.0001
Fracture of lower limb	706 (0.3)	287 (0.2)	< 0.0001

Table 1 (continued)

Characteristics	Enoxaparin prophylaxis (N = 242,474)	Unfractionated heparin prophylaxis (N = 134,384)	p-Value
Inflammatory bowel disease	1776 (1)	882 (1)	0.0075
Intubation	21,983 (9)	16,029 (12)	< 0.0001
Malignant hypertension	23,738 (10)	11,597 (9)	< 0.0001
Myocardial infarction	19,413 (9)	15,044 (11)	< 0.0001
Nephrotic syndrome	202 (0.1)	242 (0.2)	< 0.0001
Obesity	44,420 (18)	22,941 (17)	< 0.0001
Hospital characteristics			
Geographic region			< 0.0001
Northeast	37,392 (15)	46,864 (35)	
Midwest	42,200 (17)	25,048 (19)	
South	130,490 (54)	45,616 (34)	
West	32,392 (13)	16,856 (13)	
Bed size			< 0.0001
1–299	87,453 (36)	40,926 (31)	
300–499	78,027 (32)	45,961 (34)	
≥ 500	76,994 (32)	47,497 (35)	
Population served			< 0.0001
Rural	31,489 (13)	10,314 (8)	
Urban	210,985 (87)	124,070 (92)	
Teaching			< 0.0001
Non-teaching	150,371 (62)	58,685 (44)	
Teaching	92,103 (38)	75,699 (56)	

Data are presented as mean ± standard deviation or N (%) unless otherwise indicated

COPD chronic obstructive pulmonary disease, *ICU* intensive care unit

[a]Myocardial infarction, congestive heart failure, peripheral vascular disease, history of cerebrovascular accident and transient ischemic attacks, dementia, COPD, connective tissue disease, mild or moderate to severe liver disease, diabetes mellitus uncomplicated or with end-organ damage, hemiplegia, mild or moderate to severe renal disease, malignancy, and HIV positive status

Table 2 Clinical outcomes during index hospitalization and 90-day readmission periods for medically ill patients on enoxaparin and unfractionated heparin prophylaxis

	Enoxaparin prophylaxis	Unfractionated heparin prophylaxis	Enoxaparin prophylaxis (vs. unfractionated heparin prophylaxis)	
			OR[a] (95% CI)	p-Value
Index hospitalization period events				
VTE event	1144 (0.47)	1017 (0.76)	0.85 (0.78–0.94)	0.001
In-hospital mortality	8673 (3.58)	7350 (5.47)	0.91 (0.88–0.94)	<0.0001
PE-related mortality	79 (0.03)	109 (0.08)	0.67 (0.49–0.93)	0.015
90-day readmission period events				
VTE event	2867 (2.71)	1817 (3.15)	0.90 (0.85–0.96)	0.0022
In-hospital mortality	4572 (4.32)	2831 (4.90)	1.08 (1.02–1.13)	0.008
PE-related mortality	154 (0.18)	103 (0.15)	0.87 (0.66–1.14)	0.31

Data are presented as n (%) unless otherwise indicated

CI confidence interval, *ICU* intensive care unit, *OR* odds ratio, *PE* pulmonary embolism, *VTE* venous thromboembolism

[a]OR adjusted for patient characteristics (age, sex, race, payer); visit characteristics (admission source and type, and ICU admission); clinical characteristics (severity of illness, Charlson Comorbidity Index score, obesity, myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, inflammatory bowel disease, intubation, fracture of lower limb, nephrotic syndrome, and malignant hypertension); and hospital characteristics (teaching status, bed size, geographic region, and rurality)

Table 3 Economic outcomes during index hospitalization and 90-day readmission periods for medically ill patients on enoxaparin and unfractionated heparin prophylaxis

	Unadjusted mean costs			Adjusted mean estimates[a]		
	Enoxaparin prophylaxis	Unfractionated heparin prophylaxis	p-Value	Enoxaparin prophylaxis	Unfractionated heparin prophylaxis	p-Value
Index hospitalization period costs						
Total hospitalization	15,814 ± 12,953	20,282 ± 19,754	p < 0.0001	15,665 (15,386–15,907)	17,092 (16,887–17,320)	p < 0.0001
Pharmacologic prophylaxis	178 ± 190	86 ± 121	p < 0.0001	140 (136–145)	67 (65–69)	p < 0.0001
90-day readmission period costs						
Total hospitalization	9774 ± 20,449	12,270 ± 30,392	p < 0.0001	5108 (4707–5544)	5455 (5194–5921)	p < 0.0001

Data are presented in 2014US$ as mean ± standard deviation or mean (95% confidence interval) unless otherwise indicated

CI confidence interval, *ICU* intensive care unit

[a]Adjusted variables include patient characteristics (age, sex, race, payer); visit characteristics (admission source and type, and ICU admission); clinical characteristics (severity of illness, Charlson Comorbidity Index score, obesity, myocardial infarction, congestive heart failure, chronic obstructive pulmonary disease, inflammatory bowel disease, intubation, fracture of lower limb, nephrotic syndrome, and malignant hypertension); and hospital characteristics (teaching status, bed size, geographic region, and rurality)

heart failure, severe respiratory disease, and acute ischemic stroke in the respective trials. In contrast, a recent meta-analysis [21] did not find a significant reduction in VTE events between enoxaparin and UFH prophylaxis in medically ill inpatients. This meta-analysis evaluated the efficacy of all VTE prophylactic drugs in medically ill patients but included only one study [16] for direct comparison and three studies [22–24] for indirect comparisons between enoxaparin and UFH prophylaxis. Randomized clinical trials assessing VTE prophylaxis have reported inconsistent findings for reduced bleeding with enoxaparin compared with heparin. Similar to our study, a multicenter, controlled, randomized, open study of medical patients with heart failure or severe respiratory disease demonstrated less bleeding with enoxaparin [14]. A randomized double-blind study of ischemic stroke patients with lower limb paralysis resulting in bed rest also showed that enoxaparin was associated with a reduced risk of bleeding [17]. In contrast, the PREVAIL open-label study of patients with acute ischemic stroke unable to walk unassisted showed no difference in the occurrence of any bleeding between enoxaparin and UFH treatments [15].

Few studies using large real-world hospital or administrative databases have been conducted to compare effectiveness between enoxaparin and UFH thromboprophylaxis in heterogeneous medically ill inpatients [25, 26]. A 49% and 74% lower risk of VTE events was reported in two studies, which is substantially higher than the 15% reduced risk in the current study [25, 26]. Differences in the age and SOI of the study cohorts as compared with the current study might explain the greater reduction in odds of VTE events. Moreover, previous studies that investigated the association of enoxaparin prophylaxis with hospital death during index hospitalization did not find significant results [21, 25],

unlike the current study where a 9% reduced odds of hospital deaths was observed. A smaller study cohort in McGarry et al. [25], and use of direct and indirect comparisons in the meta-analysis by Al Yami et al. [21], may partially explain the differences in findings.

In this study, enoxaparin prophylaxis was also associated with lower total hospitalization costs. Despite higher medication costs, the mean adjusted total index hospital cost for the enoxaparin prophylaxis group was 2014US$1427 lower than that for the UFH group. Given that it costs around 2014US$7712–16,644 to manage one VTE event in the USA [27], thromboprophylaxis with enoxaparin might reduce the economic burden in medically ill patients at risk of VTE. This economic benefit is consistent with that observed in previous studies comparing enoxaparin and UFH [26, 28–32]. Nonetheless, the clinical significance of the association between enoxaparin and costs should be interpreted with care as the UFH cohort had longer hospitalization stays. Longer lengths of stay, major and extreme SOI, and higher CCI score could reflect a sicker status than that of the enoxaparin patients. While VTE prophylaxis guidelines generally recommend LMWH as the drug of choice for medically ill hospitalized patients, UFH is indicated in patients with renal failure (creatinine clearance < 30 ml/min). UFH has a short half-life, is predominately metabolized by the liver, and generally does not require dose adjustment with renal failure as does LMWH, particularly enoxaparin [33, 34].

The potentially beneficial effects of enoxaparin prophylaxis were also seen during the 90 days following discharge from index hospitalization. Readmitted patients who received enoxaparin thromboprophylaxis during index hospitalization had significantly fewer VTE events and lower total hospitalization costs in the readmission period than

those who received UFH during the index hospitalization. Real-world evidence studies comparing clinical and economic readmission outcomes are limited [32, 35]. Kociol et al. [35] found no statistically significant differences in 30-day post discharge outcomes in patients with heart failure, whereas a decision-analysis study by Deitelzweig et al. [32] reported findings favorable for enoxaparin prophylaxis for 2-year readmission outcomes and costs. The current study included only patients readmitted to the same index hospital within 90 days after discharge. In addition, no variables in the readmission period were captured to adjust for in the models. In addition, differences with earlier studies in the nature of study patients, readmission time period, and primary pharmacologic thromboprophylactic comparison groups [32, 35] make comparisons with the current study challenging.

This study has several limitations, many related to the inherent characteristics of a hospital administrative database. First the PHD is a hospital administrative database that relies on ICD codes and does not contain the many clinical details and laboratory values available from electronic healthcare records. Clinical details associated with VTE risk such as smoking status, prior VTE history, underlying malignancy, recent trauma/surgery, and immobility were not available, and review of medical charts was outside the scope of this study. Second, laboratory creatine clearance values were also unavailable, and it is difficult to determine whether use of UFH could be attributed to renal failure. Nonetheless, renal disease was determined by ICD codes and included in the CCI score. Thus, the possibility of unmeasured confounding or residual confounding cannot be ruled out. Lastly, inaccurate or incomplete ICD-9/10-CM diagnosis coding by hospitals could have resulted in misidentification of study-eligible patients, covariates, or VTE and PE events. It was not possible to distinguish between symptomatic and asymptomatic VTE events since VTE diagnostic testing was not captured in the PHD. As in all retrospective observational studies, patients were not randomly assigned to drug treatment, which could result in selection bias. Although efforts were taken to capture VTE events after the receipt of prophylactic drugs and to exclude subjects with VTE diagnosis within the first 2 days of index hospitalization admission, the study was not designed to determine causal relationships. Events in the follow-up period might have been underestimated because subsequent encounters may have occurred outside the index hospital. While many of the described limitations are associated with data source and study design, use of real-world data from a large geographically diverse hospital database reflects the current state of clinical and prophylactic prescribing practices with enoxaparin and UFH to prevent VTE in hospitalized medically ill patients. Moreover, studies using real-world evidence to assess clinical and economic

outcomes are scarce. These findings add to the clinical trial data that are designed under very controlled conditions.

5 Conclusions

This study provides a contemporary, real-world, US hospital-based perspective of enoxaparin and UFH thromboprophylaxis in diverse, medically ill, hospitalized patients. Enoxaparin prophylaxis was associated with a statistically significant lower odds of VTE events, in-hospital mortality, PE-related mortality, and major bleeding than was UFH. Our results highlight the need to identify patients at high risk for VTE and opportunities to optimize the selection of the appropriate thromboprophylaxis.

Declarations

Conflict of Interest S.P. Veeranki was an employee of Premier Applied Sciences, Premier Inc. at the time of the study. M. Sinha is an employee of Premier Applied Sciences, Premier, Inc. Premier Applied Sciences received funding from Sanofi US Services, Inc. to conduct this study. B. Shah is employed by and holds equity from Livongo Health and also serves as a consultant for Premier Inc., Janssen, and Medtronic. Z. Xiao was an employee of Sanofi at the time of the study and is a stockholder. A. Levorsen is an employee of and stockholder in Sanofi.

Ethics Approval The PHD is considered exempt from Institutional Review Board oversight as dictated by Title 45 Code of Federal Regulations, Part 46 of the United States, specifically 45 CFR 46.101(b)(4). In accordance with the HIPAA Privacy Rule, disclosed data from the PHD are considered de-identified per 45 CFR 164.506(d)(2)(ii)(B) through the "Expert Determination" method.

Consent to participate Not applicable.

Availability of data and material Data from the PHD are proprietary and cannot be shared externally.

Code availability Not applicable.

Authors' contributions S.P. Veeranki, Z. Xiao, and A. Levorsen were responsible for design of the study. S.P. Veeranki and M. Sinha had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis. S.P. Veeranki interpreted the study findings with assistance from Z. Xiao and B. Shah and drafted the first draft of the manuscript. All authors were responsible for critical revision of the manuscript, for important intellectual content, and provided approval of the final draft.

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