

Thromboembolism Prophylaxis in Medical Inpatients: Effect on Outcomes and Costs

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Objectives: To evaluate the real-world use of venous thromboembolism (VTE) prophylaxis among medical inpatients and the impact of VTE prophylaxis on outcomes and cost.

Study Design: Retrospective analysis of patient-level administrative claims data for medical inpatients at risk of VTE and linked outpatient data.

Methods: Data were analyzed from patients admitted to the hospital from 2005 to 2007 (calendar years) with a primary diagnosis of chronic heart failure, thromboembolic stroke, severe lung disease, acute infection, or cancer (index hospitalization), according to whether they received VTE prophylaxis or not. The number of VTE events, time to VTE event, length of hospital stay, and number of major or minor bleeding events were analyzed from the index date until the end of follow-up (180 days postdischarge) or death.

Results: Overall, 7127 of 13,293 patients (53.6%) received VTE prophylaxis. Prophylaxis significantly reduced the incidence of VTE compared with no prophylaxis (0.06% vs 3.44%, respectively; $P < .00001$) and increased the median time to VTE (182 vs 27 days, respectively). Prophylaxis also significantly reduced the incidence of VTE in the 180 days postdischarge. Readmission rates were similar between groups. Major bleeding occurred in 1.57% of patients receiving low molecular weight heparin + warfarin versus <.6% receiving any other form of prophylaxis. The development of VTE or major or minor bleeding events significantly increased total medical costs versus no VTE events ($P < .0001$) or no bleeding events ($P \leq .0003$).

Conclusions: This real-world analysis showed that thromboprophylaxis was underutilized in medical patients, even though the clinical and economic impact of VTE was significant.

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For author information and disclosures, see end of text.

Venous thromboembolism (VTE) is a significant medical problem, with an estimated 200,000 to 600,000 Americans developing VTE each year.¹ It is estimated that more than three-fourths of hospitalized patients in the United States have at least 1 risk factor for VTE and 48% have 2 or more risk factors.² VTE risk is lower in medical patients than in surgical patients, but still substantial (10%-20%).³ In addition, there is increasing evidence that medical patients are less likely than surgical patients to receive thromboprophylaxis, even when it is indicated or recommended.⁴ In the US cohort from the multinational Epidemiologic International Day for the Evaluation of Patients at Risk for Venous Thromboembolism in the Acute Hospital Care Setting (ENDORSE) study, 48% of medical patients at risk of VTE received the recommended prophylaxis, compared with 71% of at-risk surgical patients.⁴ Postoperative VTE has been clearly shown to increase length of hospital stay, medical costs, and mortality,⁵ but far less is known about the impact VTE has on medical inpatients.

The aim of this study was to analyze the effect of pharmacologic VTE prophylaxis among medical inpatients on the incidence and timing of VTE, readmission due to VTE, bleeding events, and cost of care in the 30, 90, and 180 days in the postdischarge period after the initial (index) admission.

METHODS

Subjects and Databases

This was a retrospective analysis of patient-level data from the MarketScan Hospital Drug Database (HDD) and linked outpatient files from the MarketScan Commercial and Medicare Supplemental Database from Thomson Reuters for calendar years 2005 to 2007. This is a proprietary database containing the largest collection of US employer-based patient data. Inpatient, outpatient, pharmacy, and enrollment data from MarketScan, together with linked HDD data, were used in this study. Data from 172 hospitals were identifiable for linkage in both hospital and claims databases and covered a geographically diverse area and both public and private health plans. These databases capture clinical and prescription

In this article
Take-Away Points / 295
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Web exclusive
eAppendices A-C

data for the full continuum of care, including physician office visits; hospital stays; retail, mail order, and specialty pharmacies; and carve-out care.

Hospital data comprised submitted claims linked to detailed service-level hospital bills for each admission. Outpatient claims data were matched to each admission using the following patient level identifiers: date of admission, date of discharge, age, gender, and principal diagnosis. Admissions not uniquely identified by this key set of variables were excluded.

The study population consisted of all patients admitted to hospital with a primary diagnosis of chronic heart failure (CHF), thromboembolic stroke, severe lung disease, acute infection, or cancer, based on the *International Classification of Diseases, Ninth Revision (ICD-9)* codes (see [eAppendix A](#), available at www.ajmc.com) during calendar years 2005 to 2007. This was defined as the index hospitalization. The population was grouped into 2 cohorts: those who developed VTE during index hospitalization and those who did not. VTE during hospitalization was identified by the presence of *ICD-9* codes for deep vein thrombosis (DVT; 451.1x-451.81, 451.83-451.9x, 452.xx, 453.2-453.9x) or pulmonary embolism (PE) (415.1x) on hospital records. In order to ensure that patients were not erroneously designated as having VTE, true VTE was defined as any VTE event for which anticoagulant therapy was prescribed within 15 days of diagnosis.⁶ In accordance with current privacy rule guidelines, no patient's identity or medical records were disclosed, except in compliance with applicable law.

Variables

Patient age, gender, and comorbidity data were collected at the index hospitalization. Comorbidity information included the Charlson Comorbidity Index,⁷ the Elixhauser Comorbidity Index,⁸ and a primary or secondary diagnosis (based on *ICD-9* or *ICD-9-CM* codes) of congestive heart failure, peripheral arterial disease, acute coronary syndromes, hyperthyroidism, obesity, diabetes, hypertension, ischemic or hemorrhagic stroke, noncentral nervous system systemic embolism, transient ischemic attack, catheter ablation, dyspepsia, or preperiod VTE (see [eAppendix B](#)). The preperiod began 180 days before the index event (date of hospital admission).

Outcomes were analyzed according to whether or not patients received any anticoagulant prophylaxis prior to VTE or true VTE diagnosis. In addition, the following prophylactic treatment groups were identified: low molecular weight heparin (LMWH) only; warfarin only; unfractionated hepa-

Take-Away Points

A retrospective analysis of data from medical inpatients at risk of venous thromboembolism (VTE) (n = 13,293) examined the impact of VTE prophylaxis during admission on clinical outcomes and costs:

- During the index hospitalization, 53.6% received VTE prophylaxis.
- VTE prophylaxis significantly reduced the incidence of VTE up to 180 days postdischarge and prolonged median time to VTE development.
- Significantly higher total medical costs were incurred in patients developing VTE or major or minor bleeding.
- Greater emphasis should be placed on ensuring that at-risk medical patients receive VTE prophylaxis to reduce VTE events and associated costs.

rin (UFH) only; fondaparinux; LMWH + warfarin; UFH + warfarin. The drug use observation period was defined as time from admission for the index hospitalization until 30 days after index hospital discharge.

All outcomes were measured from the index admission date up to 180 days postdischarge or death, whichever occurred first. These outcomes were: the number of VTE and true VTE events; time to the VTE event; length of hospital stay (calculated at patient level); the number of major or minor bleeding events using *ICD-9-CM* codes (see [eAppendix C](#)); the number of patients readmitted for true VTE within 30, 90, and 180 days after index hospital discharge, based on subsequent hospital admission diagnosis of true VTE, or primary or secondary diagnosis of true VTE within 1 to 2 days of subsequent hospital admission; the number of patients readmitted with major bleeding within 30, 90, and 180 days after index hospital discharge, based on subsequent hospital admission diagnosis (primary or secondary) of major bleeding, or primary or secondary diagnosis of major bleeding 1 week before or 1 week after subsequent hospital admission; discharge status (ie, home, short-term hospital stay, transfer to other facility, miscellaneous); and all-cause health-care costs paid by the patient and health plan. These costs were computed for medical services (inpatient stay, emergency department visits, and ambulatory care, including physician visits and other outpatient services), pharmacy dispensing, and total combined costs. Prices were adjusted using the annual medical care component of the consumer price index to reflect inflation between the year of the claim and 2007.

Statistical Methods

All study variables, including baseline and outcome measures, were analyzed descriptively as numbers and percentages for dichotomous and polychotomous variables, and as means, medians, standard deviations (SDs), and percentiles for continuous variables. Bivariate comparisons of baseline variables and outcomes were made using the appropriate test (*t* test, Mann-Whitney *U* test, or χ^2 test), depending on the distribution of the variable. Standardized differences were calculated. The time to VTE event was calculated using Kaplan-Meier

■ **Table 1.** Characteristics of Medical Inpatients According to Primary Diagnosis for Index Hospital Admission

Characteristic	Chronic Heart Failure (n = 1903)	Thromboembolic Stroke (n = 1931)	Severe Lung Disease (n = 4473)	Acute Infection (n = 1936)	Cancer (n = 3050)	Total (n = 13,293)
Age						
Mean (SD), years	72.00 (13.08)	71.08 (12.27)	64.50 (20.08)	64.16 (19.95)	64.40 (13.14)	66.46 (17.03)
Median, years	74 (69-78)	73 (68-77)	69 (63-74)	68 (63-73)	64 (59-68)	69 (57-74)
65 to 74 y, n (%)	429 (22.54)	460 (23.82)	1005 (22.47)	382 (19.73)	767 (25.15)	3043 (22.89)
75 to 84 y, n (%)	641 (33.68)	638 (33.04)	1224 (27.36)	456 (23.55)	306 (19.77)	3562 (26.80)
85 to 94 y, n (%)	281 (14.77)	232 (12.01)	392 (8.76)	208 (10.74)	128 (4.20)	1241 (9.34)
≥95 y, n (%)	27 (1.42)	13 (0.67)	17 (0.38)	20 (1.03)	4 (0.13)	81 (0.61)
Gender						
Male, n (%)	1067 (55.91)	991 (51.32)	32,035 (45.50)	886 (45.76)	1415 (46.39)	6391 (48.08)
Region						
Northeast, n (%)	18 (0.95)	20 (1.04)	78 (1.74)	30 (1.55)	45 (1.48)	191 (1.44)
North Central, n (%)	459 (24.12)	421 (21.80)	1199 (26.81)	465 (24.02)	527 (17.28)	3071 (23.10)
South, n (%)	1409 (74.04)	1468 (76.02)	3142 (70.24)	1420 (73.35)	2441 (80.03)	9880 (74.32)
West, n (%)	17 (0.89)	22 (1.14)	54 (1.21)	21 (1.08)	37 (1.21)	151 (1.14)
Comorbidity						
Elixhauser Comorbidity Index (≥2%), n (%)	243 (12.77)	128 (6.63)	419 (9.37)	212 (10.95)	488 (16.00)	1490 (11.21)
Charlson Comorbidity Index, mean (SD)	2.00 (1.85)	1.42 (1.55)	1.56 (1.86)	1.60 (2.07)	3.02 (2.73)	1.94 (2.17)
Congestive heart failure, n (%)	969 (50.92)	150 (7.77)	523 (11.69)	230 (11.88)	121 (3.97)	1993 (14.99)
Peripheral arterial disease, n (%)	137 (7.20)	173 (8.96)	214 (4.78)	111 (5.73)	91 (2.98)	726 (5.46)
Acute coronary syndrome, n (%)	160 (8.41)	51 (2.64)	126 (2.82)	49 (2.53)	44 (1.44)	430 (3.23)
Hyperthyroidism, n (%)	13 (0.68)	6 (0.31)	23 (0.51)	8 (0.41)	26 (0.85)	76 (0.57)
Obesity, n (%)	45 (2.36)	20 (1.04)	79 (1.77)	62 (3.20)	37 (1.21)	243 (1.83)
Diabetes, n (%)	687 (36.10)	486 (25.17)	921 (20.59)	529 (27.32)	512 (16.79)	3135 (23.58)
Hypertension, n (%)	873 (45.87)	866 (44.85)	1491 (33.33)	762 (39.36)	1210 (39.67)	5202 (39.13)
Ischemic stroke, n (%)	148 (7.78)	758 (39.25)	251 (5.61)	113 (5.84)	126 (4.13)	1396 (10.50)
Hemorrhagic stroke, n (%)	4 (0.21)	16 (0.83)	8 (0.18)	14 (0.72)	8 (0.26)	50 (0.38)
Non-CNS systemic embolism, n (%)	23 (1.21)	11 (0.57)	66 (1.48)	49 (2.53)	55 (1.80)	204 (1.53)
Transient ischemic attack, n (%)	35 (1.84)	190 (9.84)	60 (1.34)	31 (1.60)	29 (0.95)	345 (2.60)
Catheter ablation, n (%)	658 (34.58)	276 (14.29)	526 (11.76)	273 (14.10)	239 (7.84)	1972 (14.83)
Dyspepsia, n (%)	8 (0.42)	5 (0.26)	19 (0.42)	10 (0.52)	21 (0.69)	63 (0.47)
Preperiod VTE, n (%)	60 (3.15)	27 (1.40)	119 (2.66)	91 (4.70)	102 (3.34)	399 (3.00)

CNS indicates central nervous system; SD, standard deviation; VTE, venous thromboembolism.

curves and analyzed using Cox regressions. A multivariable risk adjustment model was undertaken to estimate outcome measures, incorporating age, gender, region, baseline Elixhauser Comorbidity Index, CHF, thromboembolic stroke, severe lung disease, acute infection, and cancer as confounding factors. Total costs were estimated using log transformation and general linear models, depending on the distribution and presence of heteroskedasticity.

RESULTS

Study Population

The study cohort comprised 13,293 medically ill hospitalized patients (Table 1). The most common reasons for hospitalization were severe lung disease (n = 4473; 33.65%) and cancer (n = 3050; 22.94%). The mean (SD) age of the cohort was 66.5 (17.0) years; 48% of patients were male. Patients

Table 2. True VTE, Major Bleeding, and Minor Bleeding Events Occurring During Hospitalization According to Type of Anticoagulant Prophylaxis

	No Anti-coagulant (n = 6166)	Any Anti-coagulant (n = 7127)	Warfarin Only (n = 765)	Fondaparinux Only (n = 12)	UFH Only (n = 2361)	LMWH Only (n = 2359)	LMWH + Warfarin (n = 318)	UFH + Warfarin (n = 365)
Unadjusted analysis, n (%)								
True VTE	212 (3.44)	4 (0.06) ^a	0	0	1 (0.04)	3 (0.13)	0	0
Major bleeding	42 (0.68)	37 (0.52)	2 (0.26)	0	14 (0.59)	5 (0.21)	5 (1.57) ^b	2 (0.55)
Minor bleeding	364 (5.90)	373 (5.23)	37 (4.84)	0	110 (4.66)	107 (4.54)	14 (4.40)	27 (7.40)
Risk adjusted analysis,^b %								
True VTE	2.71	0.03 ^a	0	0	0	0	0	0
Major bleeding	0.43	0.29	0.09	0	0.23	0.10	0.62 ^c	0.19
Minor bleeding	5.21	4.08	3.98	0	4.36	3.79	4.08	7.71 ^c

LMWH indicates low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

^a $P < .00001$ vs no anticoagulant.

^b $P < .005$ vs LMWH only.

^cRisk adjustment was undertaken on the total cohort only and controlled for age, gender, region, comorbid conditions, preperiod VTE, and admission diagnosis.

with CHF or stroke were older than those in other subgroups (Table 1). The cancer subgroup had the highest proportion of patients with an Elixhauser Comorbidity Index ≥ 2 (16%). Overall, 399 patients (3.0%) had experienced a VTE in the 6 months preceding the index hospitalization.

Thromboprophylaxis Used

During the index hospitalization, 7127 patients (53.6%) received thromboembolic prophylaxis and 6166 (46.4%) did not. The most commonly prescribed agents were UFH (n = 3531) or LMWH (n = 3390), followed by warfarin (n = 1629); few patients (n = 42) received fondaparinux. The duration of treatment was longest for warfarin, with a mean of 21.49 days compared with 12.98 days for fondaparinux, 6.30 days for LMWH, and 5.24 days for UFH.

Events During Hospitalization

Of the 7127 patients who received any anticoagulant prophylaxis, 4 (0.06%) developed a true VTE, compared with 212 (3.44%) of the 6166 patients who did not receive any anticoagulant prophylaxis ($P < .00001$; Table 2). Patients who did not fall into any of the 6 anticoagulant categories described in columns 3 through 8 were included in column 2, "Any Anticoagulant." The patient number for this category will therefore be greater than the total for the 6 treatment categories specified.

Overall, major bleeding developed in 37 (0.52%) patients receiving VTE prophylaxis and 42 (0.68%) receiving no prophylaxis ($P = .226$); the corresponding rates of minor bleeding were 373 (5.23%) and 364 (5.90%), respectively ($P = .0924$). With the exception of patients receiving LMWH + warfarin, who had a major bleeding rate of 1.57%, major bleeding oc-

curred in <.6% of patients receiving any of the other anticoagulant therapies. The rate of major bleeding was significantly higher in patients receiving LMWH + warfarin versus LMWH alone (1.57% vs 0.21%; $P = .0002$; Table 2). Minor bleeding occurred in 4.4% to 7.4% of patients across all groups (including those receiving no VTE thromboprophylaxis), and there were no significant differences between groups (Table 2).

Results were similar in the risk-adjusted analysis, except that the minor bleeding rate was significantly higher with UFH + warfarin versus LMWH alone ($P = .0013$; Table 2).

Events After Discharge

Postdischarge event rates are shown in Table 3. Receipt of any anticoagulant prophylaxis significantly reduced the rate of VTE occurring up to 30, 90, or 180 days after index discharge compared with no thromboprophylaxis ($P < .00001$). LMWH + warfarin was associated with a significantly increased rate of VTE at 30, 90, and 180 days postdischarge versus LMWH alone ($P < .005$). It should be noted that for each category of events, the duration of continuous enrollment post hospital discharge differed (30, 90, and 180 days); consequently, the number of patients enrolled diminished as the duration of continuous enrollment increased.

Unadjusted rates of VTE readmission were low (<1.5%) and not significantly different across the groups (Figure A). The highest rate of VTE readmission was seen in the group receiving UFH + warfarin. No patients in the fondaparinux group were readmitted with VTE. The rates of VTE readmission after risk adjustment were lower and broadly similar to the unadjusted results (Figure B), but the rate at 90 days was significantly lower in the group receiving no prophylaxis versus any prophylaxis (0.15% vs 0.26%; $P = .05$).

■ **Table 3.** True VTE, Major Bleeding, and Minor Bleeding Events Occurring up to 30, 90, or 180 Days After Discharge From Index Hospitalization, According to Type of Anticoagulant Prophylaxis

	No Anti-coagulant Drug	Any Anti-coagulant Drug (n = 7127)	Warfarin Only (n = 765)	Fondaparinux Only (n = 12)	UFH Only (n = 2361)	LMWH Only (n = 2359)	LMWH + Warfarin (n = 318)	UFH + Warfarin (n = 365)
Unadjusted analysis, n (%)								
30 days postdischarge	N = 5998	N = 6949	N = 752	N = 12	N = 2313	N = 2295	N = 309	N = 353
True VTE	215 (3.58)	53 (0.76) ^a	4 (0.53)	0	10 (0.43)	15 (0.65)	7 (2.27) ^b	2 (0.57)
Major bleeding	53 (0.88)	66 (0.95)	6 (0.80)	0	18 (0.78)	15 (0.65)	7 (2.27) ^b	8 (2.27) ^b
Minor bleeding	459 (7.65)	524 (7.54)	62 (8.24)	1 (8.33)	146 (6.31)	149 (6.49)	26 (8.41)	40 (11.33) ^b
90 days postdischarge	N = 5613	N = 6464	N = 693	N = 12	N = 2168	N = 2137	N = 291	N = 325
True VTE	201 (3.58)	95 (1.47) ^a	9 (1.30)	0	29 (1.34)	19 (0.89)	12 (4.12) ^b	6 (1.85)
Major bleeding	65 (1.16)	100 (1.55)	11 (1.59)	0	30 (1.38)	23 (1.08)	7 (2.41)	12 (3.69) ^b
Minor bleeding	556 (9.91)	678 (10.49)	91 (13.13)	1 (8.33)	187 (8.63)	204 (9.55)	34 (11.68)	51 (15.69) ^b
180 days postdischarge	N = 5203	N = 5932	N = 634	N = 11	N = 2013	N = 1963	N = 263	N = 300
True VTE	190 (3.65)	106 (1.79) ^a	14 (2.21)	0	34 (1.69)	23 (1.17)	11 (4.18) ^b	7 (2.33)
Major bleeding	86 (1.65)	122 (2.06)	14 (2.21)	0	38 (1.89)	31 (1.58)	9 (3.42) ^b	12 (4.00) ^b
Minor bleeding	647 (12.44)	818 (13.79)	113 (17.82) ^b	1 (9.09)	238 (11.82)	238 (12.12)	46 (17.49) ^b	57 (19.00) ^b
Risk-adjusted^c analysis, %								
30 days postdischarge								
True VTE	2.86	0.03 ^a	0.25	0	0.17	0.32	1.14 ^b	0.26
Major bleeding	0.70	0.29	0.37	0	0.38	0.41	1.00	0.70
Minor bleeding	7.18	4.08	7.38	7.75	6.13	6.06	8.30	11.70 ^b
90 days postdischarge								
True VTE	2.82	1.02 ^a	0.54	0	0.46	0.39	1.98 ^b	0.86
Major bleeding	1.06	1.19	1.07	0	1.04	0.82	1.59	2.43 ^b
Minor bleeding	9.57	9.95	12.18 ^b	8.04	8.42	9.09	11.80	16.48 ^b
180 days postdischarge								
True VTE	2.99	1.30 ^a	1.27	0	0.80	0.69	2.61 ^b	1.55
Major bleeding	1.54	1.60	1.39	0	1.39	1.19	2.12	2.49 ^b
Minor bleeding	12.25	13.10	16.90 ^b	8.99	11.57	11.93	17.72 ^b	19.34 ^b

LMWH indicates low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

^a $P \leq .0003$ vs no anticoagulant.

^b $P < .05$ vs LMWH only.

^cRisk adjustment was undertaken on the total cohort only, and controlled for age, gender, region, comorbid conditions, preperiod VTE, and admission diagnosis.

There were no significant differences in the unadjusted rate of major or minor bleeding occurring up to 180 days among the groups receiving single-agent anticoagulant prophylaxis, with the exception of an increase in the rate of minor bleeding with warfarin versus LMWH at 180 days (17.82% vs 12.12%; $P = .0003$). Major and minor bleeding rates were significantly increased with UFH + warfarin versus LMWH alone at all time points ($P < .005$). Risk-adjusted analyses showed broadly similar results. Unadjusted rates of readmission for major bleeding were <1% in all groups and were consistently highest in the group receiving UFH + warfarin (Figure C). The difference between the UFH + warfarin group and the LMWH alone group was statistically significant at all time points ($P < .03$). No patient receiving fondaparinux was readmitted with major bleeding.

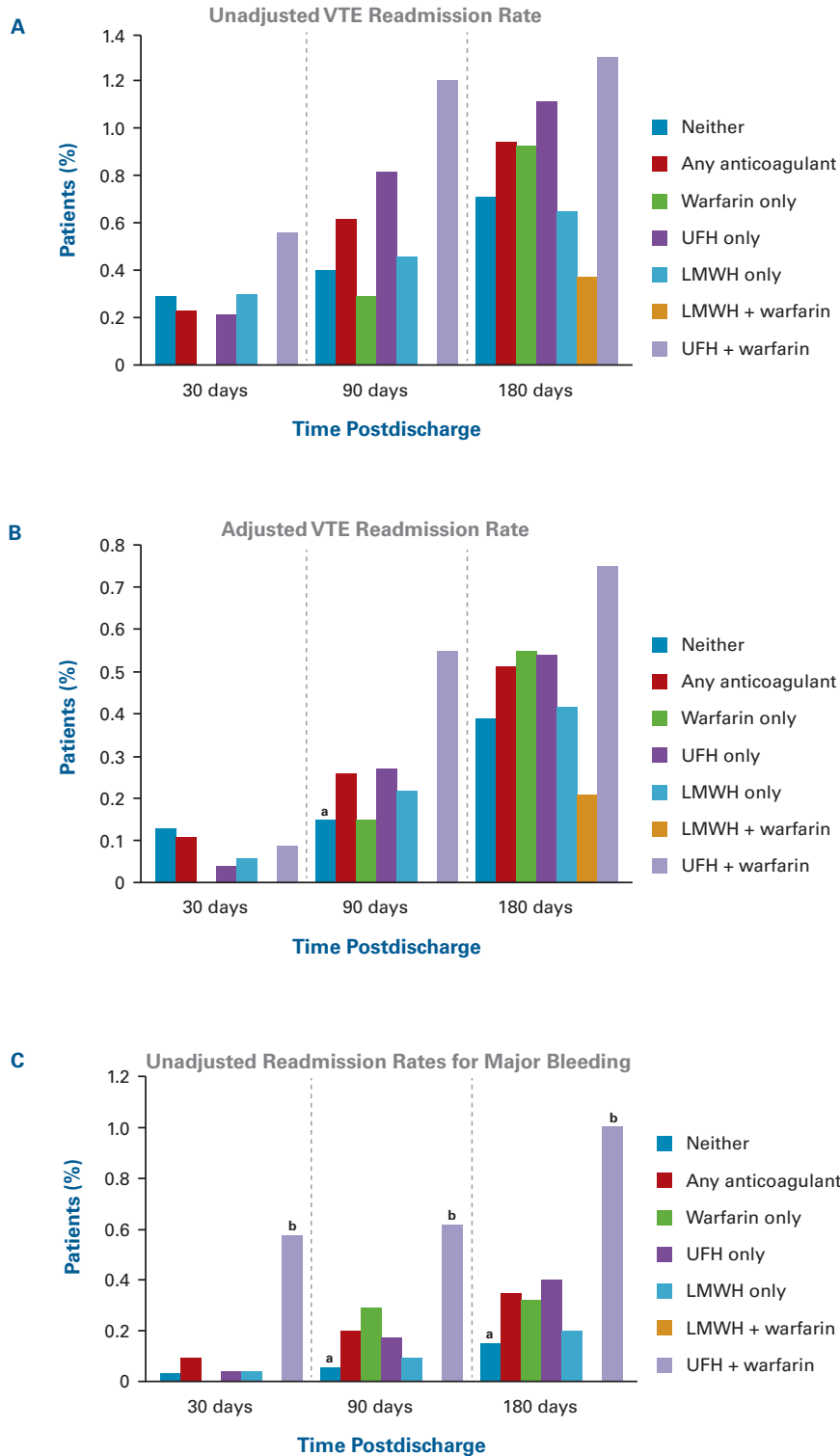
In the risk-adjusted analysis, the rate of readmission for major bleeding was 0.07% in the UFH + warfarin group at 180 days, but was otherwise 0% in all groups at all time points.

Costs

The per patient cost of medical care from admission until 30, 90, or 180 days postdischarge was significantly higher in patients who developed VTE compared with those who did not develop VTE ($P < .0001$; Table 4). Similarly, the per patient cost of medical care during these time periods was significantly higher in patients who developed major or minor bleeding compared with those who did not develop bleeding ($P \leq .0003$). Risk adjustment did not change these patterns (Table 4) as was the case in Table 3. In Table 4, for each cat-

VTE Prophylaxis in Medical Inpatients

Figure. Readmission Rates at 30, 90, and 180 Days After Discharge From Index Hospitalization



category of costs, the duration of continuous enrollment post hospital discharge differed (30, 90, and 180 days). As a result, the number of patients enrolled diminished as the duration of the continuous enrollment period increased.

Time to Events

The median time to VTE was 182 days (interquartile range 175-197) in patients who received any anticoagulant versus 27 days (interquartile range 13-35) in those who received no thromboprophylaxis. The only factors significantly associated with prolonged time to VTE in the Cox proportional hazard model were anticoagulant use ($P < .0001$) and thromboembolic stroke ($P = .0017$).

Anticoagulant use was not significantly associated with prolonged time to major ($P = .8602$) or minor bleeding ($P = .5453$) in the Cox proportional hazard model. The only factors significantly associated with prolonged time to major bleeding were female gender ($P = .0162$) and living in the North Central region of the United States ($P = .0493$ vs West). Factors significantly associated with prolonged time to minor bleeding were primary diagnoses of CHF ($P = .0068$), thromboembolic stroke ($P < .0001$), or severe lung disease ($P = .002$), and living in the North Central region of the United States ($P = .0328$).

DISCUSSION

This study shows that in a real-world setting the use of thromboprophylaxis in hospitalized medical patients reduces the risk of VTE occurring both during hospitalization and in the 180 days after discharge. Results support the benefit of VTE

LMWH indicates low molecular weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism. The risk-adjusted rate of readmission for major bleeding was 0% in all groups at all time points, except for the group receiving no anticoagulant therapy, which had a risk-adjusted readmission rate for major bleeding of .07% at 180 days postdischarge.

^a $P < .05$ vs no anticoagulant therapy.

^b $P < .05$ vs LMWH alone.

■ **Table 4.** Costs Associated With True VTE or Bleeding From Admission Until 30, 90, and 180 Days After Discharge From Index Hospitalization

Per Patient Cost	N	Mean (SD), US\$	N	Mean (SD), US\$	P	Standardized Difference (%)
VTE costs		VTE		No VTE		
Before risk adjustment						
From admission until 30 days postdischarge	268	\$30,565 (\$35,646)	12,679	\$12,511 (\$14,772)	<.00001	66.17
From admission until 90 days postdischarge	296	\$40,417 (\$40,430)	11,781	\$17,633 (\$20,741)	<.00001	70.91
From admission until 180 days postdischarge	296	\$52,248 (\$47,464)	10,829	\$24,038 (\$63,492)	<.00001	50.33
After risk adjustment						
From admission until 30 days postdischarge		\$30,572 (\$18,672)		\$12,549 (\$4753)	<.00001	132.29
From admission until 90 days postdischarge		\$40,523 (\$22,026)		\$17,698 (\$7405)	<.00001	138.91
From admission until 180 days postdischarge		\$52,157 (\$24,389)		\$24,164 (\$11,418)	<.00001	147.01
Major bleeding costs		Major bleeding		No major bleeding		
Before risk adjustment						
From admission until 30 days postdischarge	119	\$20,449 (\$19,359)	12,828	\$12,814 (\$15,646)	<.00001	43.38
From admission until 90 days postdischarge	165	\$27,142 (\$24,921)	11,912	\$18,068 (\$21,653)	<.00001	38.87
From admission until 180 days postdischarge	208	\$33,533 (\$33,432)	10,927	\$24,621 (\$63,071)	.0003	17.52
After risk adjustment						
From admission until 30 days postdischarge		\$20,553 (\$9813)		\$12,857 (\$5053)	<.00001	98.62
From admission until 90 days postdischarge		\$27,430 (\$14,162)		\$18,137 (\$7859)	<.00001	81.15
From admission until 180 days postdischarge		\$33,656 (\$18,196)		\$24,765 (\$11,974)	<.00001	57.72
Minor bleeding costs		Minor bleeding		No minor bleeding		
Before risk adjustment						
From admission until 30 days postdischarge	983	\$18,796 (\$20,641)	11,964	\$12,399 (\$15,122)	<.00001	35.36
From admission until 90 days postdischarge	1234	\$25,637 (\$29,004)	10,843	\$17,345 (\$20,567)	<.00001	32.98
From admission until 180 days postdischarge	1465	\$33,682 (\$38,061)	9670	\$23,440 (\$66,165)	<.00001	18.98
After risk adjustment						
From admission until 30 days postdischarge		\$18,828 (\$7755)		\$12,440 (\$4857)	<.00001	98.72
From admission until 90 days postdischarge		\$25,696 (\$11,435)		\$17,410 (\$7697)	<.00001	85.01
From admission until 180 days postdischarge		\$33,690 (\$14,398)		\$23,610 (\$11,873)	<.00001	76.39

SD indicates standard deviation; US\$, US dollars; VTE, venous thromboembolism.

prophylaxis generally and LMWH in particular among medical patients, which has been demonstrated in meta-analyses of randomized controlled trials.⁹⁻¹⁵ Despite guideline recommendations that all at-risk patients receive thromboprophylaxis, our data show that only 53% of patients received it, suggesting significant underuse, consistent with the US findings of the ENDORSE study.⁴ The American College of Chest Physicians (ACCP) guidelines recommend thromboprophylaxis for all acutely ill medical patients with CHF or severe respiratory disease and for those confined to bed with other VTE risk factors, including acute neurologic disease, sepsis, and active cancer.³ In the present study, based on inclusion criteria, almost all patients had one of these conditions or risk factors, so a thromboprophylaxis utilization rate of much higher than 53% would have been expected. However, the study investigators did not analyze the proportion of patients who were not confined to bed (and therefore did not meet ACCP criteria) or in whom anticoagulant therapy may have been contraindicated.

In the current study, thromboprophylaxis significantly increased the time to VTE compared with no prophylaxis. Based on the median time to VTE and the median duration of anticoagulant therapy, this analysis suggests that most VTE events occurred after discontinuation of anticoagulant therapy. A similar phenomenon was seen in the Global Orthopaedic Registry among patients undergoing hip or knee replacement, in which many patients developed VTE after prophylaxis discontinuation.¹⁶ Although at lower overall risk compared with orthopedic surgical patients, some medical patients with chronic conditions (eg, cancer, CHF, chronic obstructive pulmonary disease) may face an extended duration of thromboembolic risk because of recurring patterns of treatment, exacerbation, or immobility. This highlights the need for further research on the optimal duration of thromboprophylaxis in medical patients.³ A recent randomized, placebo-controlled study found that extending the duration of thromboprophylaxis with LMWH from 10 to 28 days significantly reduced the incidence of VTE in some subgroups

of acutely ill medical patients; eg, women aged >75 years and those with level 1 immobility.¹⁷ The fact that extended-duration prophylaxis was not more effective in other medical patient subgroups highlights the difficulty of defining an appropriate treatment duration for such a heterogeneous group.

This study identified the use of anticoagulant therapy and a primary diagnosis of thromboembolic stroke as independent predictors of a prolonged time to VTE development. Patients with thromboembolic stroke may have some protection against VTE development as a result of receiving antithrombotic/thrombolytic therapy in the acute phase and antiplatelet therapy in the postacute phase of hospitalization.

The rate of VTE recurrence was low (<3.6% at 30 days and <4.2% at 180 days across all groups). These rates compare favorably with VTE recurrence rates of 5.2% at 30 days and 10.1% at 180 days reported in a Mayo Clinic analysis published in 2000.¹⁸ This may reflect improved methods of risk stratification and treatment in our more recent cohort (2005-2007) compared with the Mayo Clinic analysis, which spanned 1966 through 1990.

The use of any VTE prophylaxis was not associated with an increased risk of major or minor bleeding compared with no prophylaxis in this study, but the use of warfarin + LMWH or UFH increased the risk of major and minor bleeding during hospitalization, respectively, compared with LMWH alone. This is not surprising, since the risk of bleeding with warfarin is increased when it is given concomitantly with other agents affecting hemostasis.¹⁹

The study analysis found that the medical cost per patient was significantly increased by the occurrence of a VTE or major or minor bleeding event. This is consistent with previous studies showing that development of VTE-incurred hospitalization costs of more than \$22,000 are substantially higher than in an age-matched control group without VTE.²⁰ VTE or bleeding events may prolong the index hospitalization or result in readmission.^{5,21-24} A number of cost-effectiveness analyses of VTE prophylaxis and treatment have shown that the direct medical cost of staying in the hospital is the major driver of overall cost.^{25,26} In addition, a claims database analysis of events after VTE treatment showed that each postindex VTE or bleeding event requiring hospitalization added approximately \$15,000 to the overall per patient cost.²¹

Limitations

As in all retrospective studies, there is a possibility of unobserved bias in our study. We have attempted to remove as much potential bias as possible by making our model more comprehensive than any in previously published studies comparing prophylaxis with no prophylaxis groups. We also used regression analysis, which is commonly used to remove ob-

served bias and has been shown to have results similar to propensity score matching.²⁷

There are also certain limitations associated with research using claims data. A claim for a prescription does not indicate whether the medication was actually taken or taken as prescribed. Over-the-counter medications or samples provided by a physician are not included in claims data, which may underestimate the true extent (and cost) of all treatments. In addition, because errors can occur during coding, the presence of a diagnostic code does not necessarily indicate the definite presence of a condition. Coding of secondary conditions may be particularly problematic. For example, the positive predictive value of ICD-9-CM codes for lower-extremity DVT or PE is only 50% when these diagnoses are not the primary indication for hospitalization,²⁸ suggesting that study investigators may have overestimated the incidence of acute VTE in this analysis. Another limitation of our analysis was that, because few patients received fondaparinux, no meaningful conclusions can be drawn about its effect on VTE incidence or recurrence.

One other limitation of the study is the inclusion of warfarin-treated patients with the LMWH or UFH groups. The current ACCP recommendation for VTE prophylaxis includes LMWH, fondaparinux, UFH, graduated compression stockings, or intermittent pneumatic compression. Warfarin is not recommended for VTE prophylaxis in medical patients. Therefore, our results might be biased if chronic warfarin management was interrupted by either therapeutic or prophylactic doses of LMWH or UFH, and the results need to be considered with this caveat.

CONCLUSIONS

This study confirms that thromboprophylaxis is underutilized in medical patients in the United States. It also shows that anticoagulant therapy reduces the incidence of and prolongs the time to VTE among a broadly representative sample of medical inpatients, but does not significantly increase risk of major or minor bleeding. Combining warfarin with LMWH or UFH does not reduce risk of VTE but does increase risk of bleeding relative to LMWH monotherapy. Risk-adjusted total healthcare costs are significantly higher for medical patients with versus without VTE, and for those who develop bleeding versus those who do not. Overall, our data show that the occurrence of VTE in medical patients not only has a major clinical impact, but it also increases the economic burden on the US healthcare system.

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