Venous Thromboembolism Clinically Detected After Hip Fracture Surgery With Prophylaxis in a Clinical Practice Setting

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Abstract

Clinical trials have shown differences in efficacy among anticoagulants used for venous thromboembolism (VTE) prophylaxis after hip fracture surgery, but the applicability of their results is limited by constraints of the clinical trial setting.

We conducted this retrospective cohort study to assess VTE after hip fracture surgery in patients who received prophylaxis with dalteparin, enoxaparin, fondaparinux, or unfractionated heparin in a hospital setting.

After adjustments were made for demographic differences, risk for VTE was significantly higher for dalteparin (odds ratio [OR], 1.4; 95% confidence interval [CI], 0.99-1.92), enoxaparin (OR, 1.4; 95% CI, 1.05-1.86), and unfractionated heparin (OR, 1.9; 95% CI, 1.39-2.58) compared with fondaparinux. These findings confirm the results of clinical trials in a real-world setting.

In 2002, approximately 315,000 adults were hospitalized for hip fracture surgery in the United States, and this number is expected to increase given the aging population.[1,2] Of all orthopedic surgeries, hip fracture surgery confers the highest risk for developing a deep vein thrombosis (DVT) or pulmonary embolism (PE), collectively known as venous thromboembolism (VTE).[3] Without thromboprophylaxis, venographically detected rates of DVT after hip fracture surgery are 46% to 60%.[4-11] Rates of fatal PE are between 1.4% and 7.5% after hip fracture surgery, with higher rates for when pharmacologic thromboprophylaxis is not used.[3,12] Because of the clinically silent nature of VTE[13] and the high risk for mortality in the absence of prophylaxis,[3,12] the American College of Chest Physicians (ACCP) recommended, in its 2004 guidelines, pharmacologic prophylaxis for VTE in hip-fracture-surgery patients with fondaparinux (grade 1A recommendation), high-dose low-molecular-weight heparin (LMWH) products (grade 1C+ recommendation), adjusted-dose vitamin K antagonists (grade 2B recommendation), or low-dose unfractionated heparin (grade 1B recommendation).[3]

Numerous controlled clinical trials support these recommendations and the ACCP level-of-evidence grading.[3] More specifically, a Cochrane review of 31 hip-fracture-surgery trials found both unfractionated heparin and LMWH to be protective against DVT, though there was insufficient evidence to conclusively state the superiority of one agent over another.[14] In addition, a clinical trial involving hip-fracture-surgery patients showed that fondaparinux was associated with a 56.4% risk reduction in the incidence of venographically detected DVT compared with enoxaparin (19.1% and 8.3%, respectively; $P<.001$).[15]

Although these trials have evaluated the efficacy and safety of various thromboprophylaxis regimens, their applicability to clinical practice has been limited because of strict inclusion and exclusion criteria, stringent dosing and drug administration requirements, and, most important, use of venographically detected DVT as a primary outcome measure. More specifically, venography is not routinely used after orthopedic surgery, and these venographically detected thrombi may be of limited clinical significance. The effectiveness of the recommended anticoagulants outside the clinical trial setting is unknown.

In the present study, we sought to determine, in a real-world setting, the incidence of clinically detected VTEs in a cohort of patients undergoing hip fracture surgery who received injectable anticoagulants to prevent VTE. Specifically, we compared VTE occurrence associated with use of fondaparinux, a factor Xa inhibitor, with that associated with either of 2 LMWHs, dalteparin and enoxaparin, or with unfractionated heparin.

Methods

Data Source

This retrospective cohort analysis was conducted with the Perspective™ database (Premier, Inc, Charlotte, NC), which includes linked medical, pharmacy, and billing data from more than 500 geographically dispersed US hospitals. This data set contains a date-stamped log of all billed items by cost accounting department, including medications and laboratory, diagnostic, and therapeutic services, as well as primary and secondary diagnoses

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for each patient. For example, type of anticoagulant used after hip fracture surgery and a subsequent DVT episode can be linked in this record. In addition, identifier-linked enrollment files provide demographic and payer information. The database is compliant with Health Insurance Portability and Accountability Act standards, and all personal identifiers are inaccessible.

Sample Selection

Patients 18 years old or older who received a primary or secondary diagnosis that required hip fracture surgery between January 2003 and March 2005 were identified for analysis through *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes 79.15 and 79.35 and *Current Procedural Terminology (CPT)* code 820. Identified hip-fracture-surgery patients were then required to receive dalteparin, enoxaparin, fondaparinux, or unfractionated heparin during their hospital stay to be eligible for the analysis.

Patients were excluded from the study if they did not have a record of dalteparin, enoxaparin, fondaparinux, or unfractionated heparin within 2 days of surgery (2 days reflects the time for the dose to be captured in data, rather than the actual administration time), received more than one anticoagulant of interest on their first day of injectable anticoagulant therapy, received heparin only at subtherapeutic prophylactic doses (ie, heparin flush or <5000 units), had an admitting diagnosis of DVT or PE, or had an outpatient visit (including a diagnosis code for DVT or PE) during the 3 months before the hip-fracture-surgery hospitalization.

In our intent-to-treat approach, patients meeting all selection criteria were then placed into treatment cohorts according to first anticoagulant used during the hospitalization. A patient's anticoagulant therapy may have been switched after treatment day 1. Reasons for switching anticoagulants could not be ascertained from the data, but a switch in therapy may have been required because of inferior efficacy or safety outcomes with the first agent. Thus, in this intent-to-treat approach, all outcomes were attributed to the first agent.

As a high proportion of VTEs occur 2 to 5 weeks after hospitalization,[3] our study period encompassed the index (initial) hip-fracture-surgery hospitalization plus 2 months of follow-up after discharge, or until in-hospital death. In addition, baseline data were collected on patients up to 6 months before their index hospitalization to assess prior hospital resource use and severity-of-illness markers.

Outcomes of Interest

The primary outcome measure was percentage of patients with a VTE during the study period, derived by calculating the proportion of patients in each anticoagulant cohort with a confirmed/coded VTE during the study period. VTEs were identified using the *ICD-9-CM* and *CPT* codes for DVT (451.11, 451.19, 451.2, 451.81, 451.9, 453.8, 453.9) and PE (415.1, 415.11, 415.19, 459.1x). Diagnostic techniques used and location of DVT (proximal vs distal) could not be ascertained from the data available.

Secondary endpoints included stratification of the primary endpoint (DVT or PE), percentage of patients with a VTE during the index hospitalization, and percentage of patients readmitted to the hospital with a coded VTE.

Comorbidities

Comorbid conditions were assessed with the Charlson Comorbidity score, Deyo modification (ie, the Charlson-Deyo score).[16,17] The Charlson Comorbidity score and its Deyo modification have been shown to be valid and reliable in numerous administrative database analyses of hospitalized and nonhospitalized patients.[17-21] The calculated Charlson-Deyo summary score assigns weights for several (1-6) major conditions. Each patient's index severity score is calculated by totaling the assigned weight for each comorbidity; the total ranges from 0 to 33 (higher scores represent a higher burden of comorbidity).

Statistical Analyses

Univariate analyses of frequencies, medians, and means were performed to describe the study population. Statistical differences were assessed with χ^2 tests of proportionality for categorical variables and analysis of variance for continuous variables. Statistical comparisons were conducted with fondaparinux as the reference group.

A stepwise parsimonious binary logistic-regression model was derived to assess differences in percentage of patients who had a VTE between fondaparinux and the other 3 injectable anticoagulants, controlling for baseline covariates that may have affected occurrence of VTE. Baseline covariates considered included age, sex, comorbidities (Charlson-Deyo score), length of stay, presence of cancer diagnosis, presence of hypercoagulable states (eg, platelet disorder), number of hospitalizations in the 6 months before the index hospitalization, mechanical ventilation, aspirin use, pneumatic compression stocking use, warfarin use, hospital type (teaching, nonteaching), hospital geographic location (Northeast, West, Midwest, South), urban versus rural hospital location, and hospital bed size. The α level of significance was set a priori at $\leq .05$. All analyses were performed with SAS software (version 9.1).

Results

Sample Population

We identified a cohort of 64,085 patients 18 years old or older who were administered one or more of the anticoagulants of interest and had the required diagnostic code for hip fracture surgery during the study period. Twenty-three percent of these patients met one or more documented exclusion criteria, which most commonly were no documented injectable anticoagulant within 2 days of surgery (n = 9240) and no recorded date of surgery (n = 3875). The final sample consisted of 49,460 patients who received dalteparin, enoxaparin, fondaparinux, or unfractionated heparin for VTE prophylaxis after hip fracture surgery.

Table. Demographic and Baseline Characteristics of Patients by Total Sample (N = 49,460) and Anticoagulant Cohort

Characteristic	Total Sample[1]	Anticoagulant Cohort[2]			
		Fondaparinux	Dalteparin	Enoxaparin	Unfractionated Heparin
No. patients (%)	49,460 (100.0%)	2551 (5.2%)	4501 (9.1%)	36,237 (73.3%)	6171 (12.5%)
Median age, years	81	80	81 (*P* = .0003)	81 (*P*<.0001)	80 (*P* = .1892)
Female, % (n)	70.6% (34,904)	72.1% (1838)	71.5% (3219), *P* = .6332	70.9% (25,647), *P* = .1710	68.1% (4200), *P* = .0002
Payer type, % (n)					
Medicare	78.5% (38,838)	79.9% (2039)	76.1% (3424)	79.1% (28,678)	76.1% (4697)
Commercial	13.4% (6609)	12.7% (324)	14.3% (642)	12.9% (4679)	15.6% (964)
Medicaid	2.9% (1424)	1.9% (49)	3.8% (170)	2.8% (1002)	3.3% (203)
Direct employee or government	1.7% (856)	2.0% (51)	1.7% (77)	1.7% (624)	1.7% (104)
Self-pay	2.2% (1068)	2.6% (66)	2.3% (102)	2.2% (810)	1.5% (90)
Other	1.3% (665)	0.9% (22)	1.9% (86)	1.2% (444)	1.8% (113)
Admission type, % (n)					
Emergency room or urgent /trauma center	90.4% (44,708)	91.0% (2322)	91.3% (4111)	89.9% (32,576)	92.4% (5699)
Elective	6.7% (3295)	7.0% (179)	5.0% (226)	7.0% (2536)	5.7% (354)
Other/Not available	3.0% (1457)	2.0% (50)	3.6% (164)	3.1% (1125)	1.9% (118)
Fracture location, % intertrochanteric[3]	38.6%	39.5%	38.7% (*P* = .4948)	35.8% (*P* = .0010)	39.9% (*P* = .6073)
Mean Charlson–Deyo Comorbidity score[4] (±SD)	1.4 (±1.7)	1.3 (±1.6)	1.3 (±1.6), *P* = .7426	1.4 (±1.7), *P* = .0009	1.5 (±1.8), *P*<.0001
% patients switched anticoagulant therapies after day 1	—	4.7%	4.0%	2.8%	32.1%
Mean stay in days (±SD)	6.8 (±6.0)	5.8 (±4.0)	6.3 (±4.9), *P* = .0009	6.6 (±5.5), *P*<.0001	8.4 (±8.9), *P*<.0001
Mean no. hospitalizations 6 months before index visit (±SD)	0.12 (±0.43)	0.13 (±0.5)	0.11 (±0.4), *P* = .1158	0.13 (±0.4), *P* = .8235	0.11 (±0.4), *P* = .2145
% received warfarin (n)	9.4% (4653)	8.6% (218)	7.2% (324), *P*<.0415	8.6% (3128), *P* = .8806	15.9% (983), *P*<.0001
% received aspirin (n)	13.9% (6890)	9.1% (232)	12.6% (567), *P*<.0001	13.7% (4951), *P*<.0001	18.5% (1140), *P*<.0001
% required mechanical ventilation (n)	0.1% (38)	0% (0)	0.04% (2), *P* = .0494	0.08% (28), *P* = .0078	0.13% (8), *P* = .1598
% using compression stockings (n)	54.1% (26,776)	57.6% (1469)	56.4% (2538), *P* = .3292	55.6% (20,163), *P* = .0562	42.2% (2606), *P*<.0001

[1]Percentages may exceed 100% because of rounding.
[2]Tests of significance: analysis of variance for continuous variables; χ^2 for categorical variables; *P*s represent differences between fondaparinux and other anticoagulants.
[3]Versus nonintertrochanteric. *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes for intertrochanteric: 820.21, 820.31.
[4]Range 0-29 (higher scores indicate higher comorbidity).

The baseline characteristics of the study population are described in the Table. Almost three fourths of the population received enoxaparin (n = 36,237, 73.3%), and 5.2% (n = 2551) of the population received fondaparinux. Median age of all patients was 81 years, and 70.6% were women. The most common payer source for this elderly population was Medicare (78.5%). Nine of 10 admissions were to the emergency department or another urgent care facility, and 38.6% of fractures were specifically coded as intertrochanteric fractures. Mean Charlson-Deyo Comorbidity score was 1.4 (SD, 1.7), indicating a low overall burden of comorbidity. Mean hospital stay was 6.8 days (SD, 6.0 days), with patients receiving fondaparinux spending the least time (5.8 days; SD, 4.0 days) of all the cohorts (*P*<.001). Patients in the unfractionated heparin group were more likely to be treated concurrently with aspirin or warfarin compared with the other groups (*P*<.0001 vs fondaparinux).

During their inpatient stay, 90% of the patients in the fondaparinux group received 2.5 mg/d, and mean duration of therapy was 4.0 days. The most common doses in the enoxaparin group were 40 mg/d (40% of patients) and 60 mg/d (26%), and mean duration of therapy was 4.7 days. In the dalteparin group, 26% of patients received 2500 units/d, 58% received 5000 units/d, and mean duration of therapy was 4.6 days. The low-dose prophylaxis regimen was given most commonly in the unfractionated heparin group; 73% of patients in this group received 15,000 units/d or less, and mean duration of therapy was 4.6 days.

Primary Outcome

Of the total eligible population, 1578 (3.2%) had a VTE during the study period. As shown in Figure 1, significantly fewer patients in the fondaparinux group had a VTE (2.0%, n = 50, *P*<.01) compared with patients in the other groups—which translates to a relative VTE risk reduction of 37.4% versus dalteparin (95% CI, 12.7%-60.5%) 34.3% versus enoxaparin (95% CI, 12.9%-51.2%), and 60.5% versus unfractionated heparin (95% CI, 44.3%-75.4%).

After baseline covariates were controlled for, as previously described, patients in the fondaparinux group were found to be least likely to have a VTE during the study period. The odds ratios (ORs) for having a VTE for each anticoagulant (vs fondaparinux) were 1.4 for dalteparin (95% CI, 0.99-1.92; *P* = .0582), 1.4 for enoxaparin (95% CI, 1.05-1.86; *P* = .023), and 1.9 for unfractionated heparin (95% CI, 1.39-2.58; *P*<.0001). Other model variables that significantly increased the risk for VTE by at least 20% included hypercoagulable state (OR, 2.3; 95% CI, 1.45-3.58), cancer diagnosis (OR, 1.3; 95% CI, 1.06-1.52), warfarin use (OR, 1.2; 95% CI, 1.05-1.45), and hospital

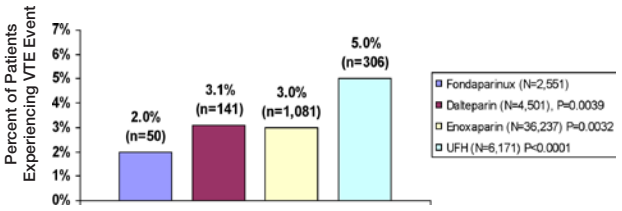

Figure 1. Percentage of patients who had a venous thromboembolism after hip fracture surgery by injectable anticoagulant during entire study period.

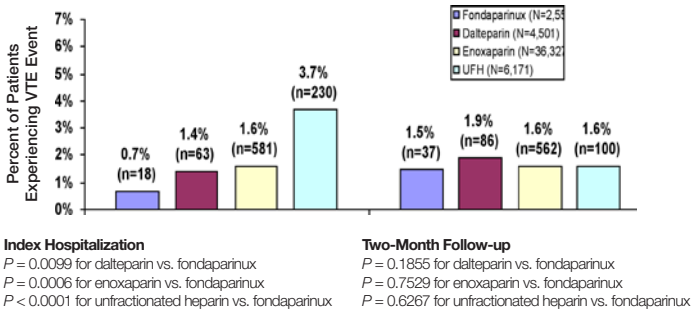

Figure 2. Percentage of patients who had a coded venous thromboembolism during hospitalization for hip fracture surgery and within 2 months after hip fracture surgery by injectable anticoagulant.

geography (Northeast [OR, 1.4; 95% CI, 1.17-1.57] and Midwest [OR, 1.3; 95% CI, 1.10-1.45] vs South). No variables significantly decreased risk for VTE.

Secondary Outcomes

Sixty-three percent of all VTEs were recorded as DVT only and 28% as PE only; the other 9% were recorded as DVT plus PE. Percentage of patients who had a coded DVT was significantly lower in the fondaparinux group (1.3%) than in the dalteparin (2.5%), enoxaparin (2.1%), and unfractionated heparin (3.4%) groups (P<.001 for all). Percentage of patients who had a PE was similar in the fondaparinux, dalteparin, and enoxaparin groups (0.9%, 0.9%, and 1.1% respectively), but significantly (P<.001) more patients in the unfractionated heparin group had a PE (1.9%).

Percentage of patients who had a coded VTE during their initial hospitalization was 1.8% overall (n = 892) and was significantly lower for patients in the fondaparinux group than for patients in the other groups (P<.01) (Figure 2). During the 2 months after hospital discharge, 785 patients (1.6%) had a VTE that necessitated readmission. Percentage of readmissions for VTE was again lowest for patients in the fondaparinux group than for patients in the other groups, but the difference was not significant (Figure 2).

Discussion

In this large retrospective database analysis, we found that significantly fewer patients in the fondaparinux group, compared with patients in the dalteparin, enoxaparin, and unfractionated heparin groups, had a VTE during the study period, which spanned the index hospitalization through 2 months after discharge. This significant VTE relative risk reduction for fondaparinux (34.3%-60.5% vs the other anticoagulants) confirms the randomized, double-blind clinical trial results in hip fracture patients in which fondaparinux was associated with a 56.4% (95% CI, 39.0%-70.3%) risk reduction compared with enoxaparin[15] and extends the conclusions to a naturalized (non–clinical trial) setting. Further, the VTE rates of 2% to 5% are consistent with the 1% to 9% rates found in other epidemiologic hip fracture studies involving patients who received a variety of preventive therapies.[12,22,23] Results of the multivariate analysis showed that factors other than anticoagulant used for prophylaxis also had a significant impact on study outcome. As reasonably expected, hypercoagulable state and cancer diagnosis independently increased risk for VTE. More surprising, however, warfarin use and hospital geography were associated with increased occurrence of VTE—perhaps pointing to inappropriate conversion to warfarin (ie, discontinuation of LMWH before reaching therapeutic international normalized ratio levels) or subtherapeutic doses. Other factors, such as patient age, sex, comorbidities, and hospital type, did not significantly affect the primary outcome. It is important to note that, in our analysis, factors independently affecting the outcome were statistically controlled for.

PE rates were low in our study (0.9%-1.9%), as in studies assessing symptomatic PEs (0.2%-1.7%).[15,24-27] With such low rates, it was difficult to detect any significant differences among the anticoagulants used in our study or in a comparative clinical trial.[15] However, DVT rates, which were significantly (P<.001) lower in our fondaparinux group, were the primary driver for differences in overall VTE, and these rates are important, as DVTs are associated with substantial morbidity.[3]

There are distinctions between earlier fondaparinux hip fracture trials[15,28] and our analysis. The primary outcome in our analysis was clinically detected (ie, symptomatic) VTE. This is a valid[15,28-32] and practical endpoint, as patients in the United States are not routinely screened for VTE. Randomized clinical trials have traditionally selected venographically detected VTE as the primary outcome measure, and they were not designed to detect differences in symptomatic VTE rates.[15,29-32] This fact explains why our VTE rates are lower than the 8.3% to 19.1% in these clinical trials.[15] However, our rates are similar to the 1.34% (95% CI, 1.04-1.64) found for symptomatic VTE in a sample of 6860 hip fracture patients, of which almost all (97.3%) received thromboprophylaxis with LMWH.[33] Several meta-analyses have demonstrated that the magnitude of reduction is similar for venographically detected VTEs and symptomatic VTEs, and our study results are consistent with these findings.[13,34,35] We were still able to identify an independent and significant VTE risk reduction with fondaparinux versus both LMWHs and unfractionated heparin.

Our study and clinical trials also differ in study duration. In the majority of orthopedic clinical trials involving hip fracture surgery, the primary assessment for VTE ended

on day 11.[15,29-32] However, because 45% to 80% of all symptomatic VTEs occur after hospital discharge, in the 2 to 5 weeks after surgery,[3] our analysis extended past the index hospitalization and ascertained VTE rates over the 2 months after discharge for the initial surgery. In this study, we have provided essential documentation of the effectiveness of thromboprophylaxis past the initial 11 days and, in particular, for fondaparinux (the only medication indicated for both initial and extended VTE prophylaxis after hip fracture surgery) in comparison with dalteparin, enoxaparin, and unfractionated heparin.

This study has several strengths. Our sample of more than 49,460 patients is larger than that in any hip-fracture-surgery thromboprophylaxis study and provides important information that complements and extends existing thromboprophylaxis data.[15,28,30,31] This large sample size confers statistical power, allowing detection of significant differences in infrequently occurring events. In addition, the size of the study population allowed us to control for multiple clinically relevant confounders, such as severity of illness and process of care. Together, these factors make the findings robust. These results are likely generalizable not only because they represent typical clinical practice but also because the geographies of the contributing hospitals are diverse. Our population, as shown by its demographics, was representative of patients typically undergoing hip fracture surgery in the United States.[33,36-39]

This study had several limitations that warrant discussion. First, the design was retrospective and nonrandomized, so causality is difficult to ascribe. However, only through retrospective database analyses can we collect a sufficiently large sample in a time-efficient manner to facilitate the analyses we completed. It is important to note that illness severity, as measured with Charlson Comorbidity scores, did not vary clinically between treatment groups. Further, the risk adjustment methodology we used can help minimize this bias in studies in which patients are not randomly assigned to treatment.[40]

Second, the quality of the administrative data entered into and extracted from the database may have affected statistical differences. There may have been overreporting or underreporting of VTEs. However, it seems unlikely that choice of prophylactic agent affected proper coding of a VTE.

Third, we likely missed some late-occurring VTEs in patients who may not have returned to a Premier-affiliated institution for postdischarge events. Similarly, VTE prophylaxis methods used outside the index hospitalization could not be captured. Again, these limitations should not have been a function of thromboprophylaxis therapy, but this possibility cannot be excluded. However, these limitations would not have affected the rates of VTE during the index hospitalizations, which were significantly reduced for patients in the fondaparinux group. In addition, comorbidities were ascertained retrospectively through longitudinal tracking and were limited to 6 months before study entry and to data collected by hospitals reporting to the data set. This may have underrepresented comorbidities.

Fourth, an important factor that we did not assess is bleeding incidence, which may have additional safety implications for anticoagulants and would be worthy of another evaluation using this hospital database.

From an economic perspective, small differences in the absolute risk for VTE confer positive financial benefit to third-party payers and health care systems. Inpatient hospitalization for a single VTE can range in cost from $7712 (DVT only) to $12,200 (DVT plus PE).[41] Compared with no prophylaxis, prophylaxis after major orthopedic surgery has consistently been shown to be cost-effective,[42-45] and LMWHs have been shown to be much more cost-effective or cost-saving than unfractionated heparin.[42,46-50] In this study, length of hospital stay was significantly ($P<.001$; Table) shorter for patients in the fondaparinux group than for patients in the other groups, and patients in the fondaparinux group had lower VTE rates for the index hospitalization and for the entire study period, encompassing the 2 months after hospital discharge.

Conclusions

As shown in our analysis, compared with dalteparin, enoxaparin, and unfractionated heparin, fondaparinux is associated with the lowest rate of clinically diagnosed VTE in hip-fracture-surgery patients both for the index hospitalization for the surgery and for 2 months after hospital discharge. This finding confirms the results of the randomized, controlled clinical trials of fondaparinux and is independent of multiple potential cofactors that alter the risk for VTE.

Authors' Disclosure Statement

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