

## Outpatient Treatment of Venous Thromboembolism with Low-Molecular-Weight Heparin: An Economic Evaluation

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### Abstract

**Background:** The development of low-molecular-weight heparins (LMWHs) has made it possible to shift treatment of deep vein thrombosis (DVT) from inpatient to outpatient settings, thereby saving costs and improving patient quality of life.

**Objective:** To quantify the economic benefits of early discharge of patients treated for DVT with LMWH using data pooled from multiple healthcare plans.

**Methods:** Data sources were integrated medical and pharmacy claims paid by 37 US health plans (the PharMetrics Integrated Outcomes Database, PharMetrics, Inc., Watertown, MA). Hospitalized patients discharged with a diagnosis of DVT were selected and grouped according to the anticoagulation therapy they received after discharge. Outcomes and costs of DVT treatment were assessed over a 1-year period.

**Results:** Patients discharged on the LMWH enoxaparin and warfarin spent 2.6 fewer days in the hospital than those discharged on warfarin alone ( $P < .0001$ ), resulting in cost savings of \$1911 per patient. Mean costs of outpatient management of DVT, including pharmacy and medical services, were \$901 higher in the enoxaparin/warfarin cohort, but rate of readmission was lower (6.7% versus 9.0%;  $P < .05$ ) and hence subsequent inpatient costs were reduced by \$140 per patient. Total cost savings in the enoxaparin/warfarin cohort, net of higher outpatient costs, were \$1151 per patient.

**Conclusions:** Outpatient anticoagulation therapy for DVT with enoxaparin and warfarin is associated with earlier hospital discharge, fewer readmissions, and lower total DVT-related costs compared with warfarin monotherapy.

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Deep vein thrombosis (DVT) is a frequent complication of major orthopedic and abdominal surgery, and is related to other conditions that cause prolonged immobility.<sup>1-3</sup> As many as 2 million cases of DVT occur annually in the United States, many of which require hospital admission or extended stays among patients already hospitalized.<sup>1</sup> In addition to long-term impairment of peripheral circulation, DVT is also a source of emboli that eventually lodge in the pulmonary arteries.<sup>1</sup> An estimated 600,000 cases of pulmonary embolism (PE), 10% of them fatal, occur annually in the United States.<sup>4,5</sup>

The current standard of care for DVT is inpatient anticoagulation therapy, involving the use of either intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) in combination with warfarin. According to current treatment guidelines, once an international normalized ratio (INR) of more than 2.0 has been attained, heparin is discontinued while oral warfarin therapy is continued for 3 to 6 months, depending on the etiology of the DVT.<sup>3</sup>

Anticoagulation with UFH involves unpredictable dose response, and hence requires close monitoring.<sup>3</sup> Patients treated with UFH are typically confined to the hospital for the duration of therapy, at least 4 to 5 days. In contrast, LMWHs are better absorbed, have a more predictable dose response and a longer half-life than

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UFH, and have been approved for outpatient use.<sup>6</sup> Hence, use of LMWH to treat DVT affords the option of earlier discharge, or even avoidance of hospital admission altogether.<sup>6-9</sup> In addition to the benefit of many patients being treated at home rather than in an institution, the use of LMWH results in significant cost savings to hospitals and health insurers.<sup>7,8</sup>

Previous pharmacoeconomic studies of outpatient treatment of DVT have been conducted in clinical trial settings or in limited numbers of institutions.<sup>7,8</sup> The present study was undertaken to quantify the economic benefits of early discharge of patients treated for DVT with LMWH using data pooled from managed health-care plans throughout the United States.

## Methods

**Overview.** Data for this study were obtained from the PharMetrics (Watertown, MA) Integrated Outcomes Database, which includes longitudinal, integrated, and complete medical and pharmacy claims histories on more than 22 million members of 37 health plans in the United States. Provider claims submitted to the health plans for reimbursement provide information on diagnoses associated with healthcare encounters, therapeutic and diagnostic procedures performed, prescription drugs dispensed, and amounts charged and reimbursed for these services.

**Patient Selection.** Patients selected for the study had an overnight hospital stay of at least 1 day with a discharge diagnosis of DVT. This stay was considered their "index" hospitalization. Patients were excluded from the analysis if they were not enrolled continuously for 6 months before and 12 months after the index hospitalization, if their discharge regimen was not consistent with current guidelines,<sup>3</sup> if they had missing data on the costs of DVT-related treatment, or if their total DVT-related costs were suspect because of extremely high values (>5 standard deviations in excess of the mean).

**Treatment Cohorts.** Patients were assigned to treatment cohorts based on

their initial anticoagulation therapy, including warfarin, UFH, or any LMWH, received after discharge. As noted above, patients whose treatment did not conform to guidelines, including use of LMWH without concomitant warfarin, were excluded from the analysis.

**Measures.** All patients included in the analysis were observed for 12 months from the date of their index hospitalization. Primary outcome measures of interest included the length and cost of the index hospitalization; costs of outpatient DVT treatment after discharge; and occurrence and cost of readmissions for DVT. Costs were measured in terms of payments made to providers for services associated with a diagnosis of DVT and for dispensing of prescriptions for anticoagulant agents. Readmissions for DVT were determined based on principal diagnoses recorded on claims submitted by hospitals. Because hemorrhage is a potential hazard of anticoagulation therapy, occurrence of readmission for hemorrhage was a secondary outcome.

Because patients were admitted to their index hospitalization for a range of illnesses and elective surgeries, and often developed DVT while in the hospital, costs varied for inpatient services unrelated to the treatment of DVT. The focus of analysis was therefore on the difference in the length of the index hospital stay (in days) between treatment cohorts. Associated cost differences were then estimated by multiplying the length of stay difference by the average per diem cost of hospital care.

For the purpose of assessing baseline characteristics and disease severity, medical utilization information was also captured for the 6-month period before the index hospitalization.

**Data Analyses.** Means and frequency distributions of baseline characteristics and outcome variables were compared between the study cohorts. Student's *t* tests were performed to assess the significance of pairwise differences between treatment cohorts. Multiple linear regres-

**Table 1.** Patient Demographics

Anticoagulant Therapy After Discharge	Number of Patients	Mean Age (yrs) ± SD	Age Distribution (yrs)			Female (%)
			< 40 (%)	41-64 (%)	≥ 65 (%)	
Warfarin only	1696	53.9 ± 13.9	280 (16.5)	1112 (65.6)	304 (17.9)	954 (56.3)
Heparin only	13	50.9 ± 10.5	2 (15.4)	10 (76.9)	1 (7.7)	5 (38.5)
Enoxaparin/warfarin	164	47.8 ± 13.7	47 (28.7)	107 (65.2)	10 (6.1)	88 (53.7)
Heparin/warfarin	16	54.1 ± 13.7	3 (18.8)	10 (62.4)	3 (18.8)	12 (75.0)
No discharge therapy	1577	52.9 ± 14.9	288 (18.3)	1049 (66.5)	240 (15.2)	892 (56.6)

SD = standard deviation.

sion was used to control for baseline demographics and comorbidities that may have influenced study outcomes.

**Results**

**Patients.** As shown in **Table 1**, 3466 patients met the study eligibility requirements and were included in the analysis. The most frequent anticoagulation therapy used for outpatient treatment of DVT was warfarin alone (n = 1696), followed by enoxaparin in combination with warfarin (n = 164), heparin with warfarin (n = 16), and heparin alone (n = 13). Approximately 45% of patients (n = 1577) had no documented discharge anticoagulation therapy.

Mean age was about 53 years and 56% of patients were women. Most were from the South or Midwest, reflecting the distribution of health plans in the PharMetrics database (**Table 2**). Health maintenance organizations (HMOs) accounted for 46% of patients; 32% were

in other managed healthcare plans such as preferred provider organizations or point-of-service plans (**Table 3**). Compared with other cohorts, patients treated with enoxaparin and warfarin were somewhat younger, more frequently from the Midwest, and more frequently enrolled in HMOs.

**Index Hospitalization.** Average length of stay for the index hospitalization in the enoxaparin/warfarin cohort was 2.6 days shorter than in the warfarin alone cohort and 3 days shorter than in the cohort with no documented treatment ( $P < .0001$  for both comparisons) (**Table 4**). These differences remained unaltered after adjustment for between-group differences in age, sex, and comorbidities. These differences in favor of enoxaparin tended to increase with age and were larger in HMOs than in other plan types (**Tables 4 and 5**).

**Table 2.** Distribution of Patients by Geographic Region

Anticoagulant Therapy After Discharge	Number of Patients	Region			
		Northeast (%)	Midwest (%)	South (%)	West (%)
Warfarin only	1696	122 (7.2)	559 (33)	874 (51.5)	141 (8.3)
Heparin only	13	1 (7.7)	3 (23.1)	8 (61.5)	1 (7.7)
Enoxaparin/warfarin	164	11 (6.7)	85 (51.8)	46 (28.1)	22 (13.4)
Heparin/warfarin	16	1 (6.3)	5 (31.3)	10 (62.5)	0 (0.0)
No discharge therapy	1577	64 (4.1)	501 (31.8)	762 (48.3)	250 (15.8)

**Table 3.** Distribution of Patients by Plan Type

Anticoagulant Therapy After Discharge	Number of Patients	Plan Type				
		HMO (%)	Indemnity (%)	PPO (%)	POS (%)	Other (%)
Warfarin only	1696	864 (50.9)	276 (16.3)	277 (16.3)	241 (14.2)	38 (2.3)
Heparin only	13	6 (46.1)	5 (38.5)	1 (7.7)	1 (7.7)	0 (0.0)
Enoxaparin/warfarin	164	101 (61.6)	15 (9.1)	17 (10.4)	26 (15.8)	5 (3.1)
Heparin/warfarin	16	11 (68.8)	2 (12.5)	0 (0.0)	3 (18.7)	0 (0.0)
No discharge therapy	1577	608 (38.6)	356 (22.6)	383 (24.3)	158 (10.0)	72 (4.5)

HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization.

**Table 4.** Average Length of Stay (Days) for Index Hospitalization, by Age

Anticoagulant Therapy After Discharge	Age (yrs)				P*
	All	≤ 40	41–64	≥ 65	
Warfarin only	6.8	6.7	6.8	7.1	.0001
Heparin only	5.1	6.0	4.7	7.0	.29
Enoxaparin/warfarin	4.2	4.6	4.1	3.2	—
Heparin/warfarin	8.3	9.0	8.8	5.7	.002
No discharge therapy	7.2	7.1	7.0	8.3	.0001

\*Versus enoxaparin/warfarin, Student's *t* test.

**Table 5.** Average Length of Stay (Days) for Index Hospitalization, by Plan Type

Anticoagulant Therapy After Discharge	Plan Type			
	HMO (n = 1610)	Indemnity (n = 662)	PPO (n = 681)	POS (n = 435)
Warfarin only	7.05	6.08	6.55	6.94
Heparin only	6.50	4.00	5.00	2.00
Enoxaparin/warfarin	4.08	4.07	4.59	4.35
Heparin/warfarin	8.55	8.00	—	7.33
No discharge therapy	7.75	7.10	6.65	6.66

HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization.

Mean per diem payments for all index hospital stays were \$735. Multiplied by the observed differences in length of stay between treatment cohorts, this number yielded cost differences of \$1911 between

enoxaparin/warfarin and warfarin alone, and \$2205 between enoxaparin/warfarin and no documented treatment. Cost comparisons were calculated only for statistically significant differences in length of stay.

**Outpatient Treatment of Deep Vein Thrombosis.** Table 6 presents costs of outpatient treatment for DVT during the year after the index hospitalization. The enoxaparin/warfarin cohort had outpatient pharmacy costs related to dispensing of anticoagulation therapy that were \$319 higher than the warfarin-only cohort and \$405 higher than the cohort with no documented treatment ( $P < .0001$  for both comparisons). During the same period, the enoxaparin/warfarin cohort had costs of other DVT-related outpatient services that were higher by \$581 and \$776, respectively, compared with the warfarin-only and initially untreated cohorts.

**Readmissions for Deep Vein Thrombosis and Pulmonary Embolism.** The occurrence and cost of readmissions for treatment of DVT and PE during the year after the index hospitalization are provided in Table 7. The enoxaparin/warfarin cohort had a 26% lower rate of readmission compared with the warfarin-only group and a 32% lower rate compared with the initially untreated group ( $P < .05$  for both comparisons). Reflecting these differences in readmission rates, costs of inpatient treatment of DVT and PE in the year after the index hospitalization were lower in the enoxaparin/warfarin cohort by \$140 compared with warfarin alone and \$275 compared with no initial therapy.

**Total Deep Vein Thrombosis-Related Costs.** Total DVT-related costs, including the index hospitalization, outpatient treatment of DVT, and readmission for DVT or PE, were lower in the enoxaparin/warfarin cohort by \$1151 compared with the warfarin-only cohort, and \$1227 compared with the initially untreated cohort.

**Readmission for Hemorrhage.** A total of 35 patients (1%) experienced a hemorrhage requiring hospitalization during the year after the index hospitalization. One of these events occurred in the enoxaparin/warfarin cohort (a rate of 0.6%), 14 in the warfarin-only cohort (0.83%), and 20 in the initially untreated cohort (1.27%). None occurred in the heparin/warfarin or heparin-only cohorts. No statistically significant differences were found among the cohorts in the rate of readmission for hemorrhage.

**Discussion**

Retrospective analysis of health insurance claims from 37 health plans in the United States has shown that outpatient anticoagulation therapy for DVT with enoxaparin and warfarin is associated with earlier discharge from hospital, fewer readmissions, and lower total DVT-related costs compared with warfarin monotherapy or no anticoagulant agent. Hemorrhage was a rare event in all treatment cohorts, indicating that outpatient anticoagulation is safe.

The findings of the present study are consistent with previous studies that have examined the clinical and economic outcomes of outpatient treatment of DVT with LMWH.<sup>6-9</sup> For example, Levine et al<sup>6</sup> reported that patients receiving LMWH therapy for DVT in the hospital before being sent home on LMWH were discharged 4.3 days earlier than those treated with UFH. Patients treated with LMWH also had 24% fewer recurrences over 90 days following treatment initiation than the UFH group.<sup>6</sup> Although the finding by Levine et al was not statistically significant, the present study was confirmatory as it showed a similar (26%) and significant reduction in the recurrence rate over

**Table 6.** One-Year Outpatient Costs of DVT/PE Treatment, by Cost Category

Anticoagulant Therapy After Discharge	Cost Category (\$)		
	Outpatient*	Rx	Total*
Warfarin only (n = 1696)	773	213	986
Heparin only (n = 13)	1349	306	1655
Enoxaparin/warfarin (n = 164)	1354	532	1886
Heparin/warfarin (n = 16)	454	128	582
No discharge therapy (n = 1577)	578	127	705

\*Includes emergency department. DVT = deep vein thrombosis; PE = pulmonary embolism; Rx = prescriptions.

1 year. Spyropoulos et al<sup>8</sup> reported cost savings of \$2248 per patient from outpatient treatment of DVT with LMWH compared with inpatient treatment with UFH, about twice the amount reported in the present study and consistent with the Canadian results of O'Brien et al<sup>7</sup> (based on the Levine et al study), who reported savings of Can \$3045 per patient.

It was noteworthy that the enoxaparin/warfarin cohort included a higher percentage of HMO patients than the other cohorts. This difference suggests that some HMOs may have implemented programs to promote outpatient treatment of DVT with LMWH as a cost-saving measure. Although the present study focused on early discharge among patients initially treated for DVT in the hospital, it is possible that some cases of DVT were treated entirely on an outpatient basis.<sup>6-9</sup> If so, the estimated cost savings reported here may substantially understate the benefits of outpatient treatment.

The presence of a large cohort of patients (45%) who were not initially treated after discharge from their index hospitalization was surprising. A number of factors may be involved. First, any drugs dispensed from hospital pharmacies would not be captured in the claims histories of the study patients. It is possible that some patients were sent home with a supply of warfarin dispensed by the hospital pharmacy and did not subsequently fill any prescription at a retail pharmacy. In fact, the warfarin-only and "untreated" cohorts were similar in their demographic composition and their average length of stay. Second, it is possible that some patients were discharged with a prescription for an anticoagulant but failed to comply with the prescribed treatment plan and never filled that prescription. Finally, some patients may have had contraindications to anticoagulant therapy, such as those with preexisting bleeding disorders. Indeed, the latter possibility may be supported by the slightly higher rate of readmission for hemorrhage in the untreated group compared with treated patients.

This study shares the limitations of all retrospective, claims-based investigations.

Because the data reflect clinical practice in the community, rather than a clinical research protocol, differences between the groups in demographic and clinical characteristics may have affected outcomes, and would require more detailed medical records to assess thoroughly. For example, patients treated with enoxaparin and warfarin were younger than those receiving other therapies, and may have been healthier on average. However, study findings stood up to multivariate statistical analyses designed to control for measurable demographic and clinical differences between treatment cohorts. Also, consistent results were observed across all age groups and plan types.

The standard hospital claim form for submission to a health insurer (the Uniform Bill, 1992 version, or UB-92) records department-level charges but does not itemize the specific drugs and services provided to patients. Therefore, data were not available on the administration of anticoagulation therapy during the index hospital stay for study patients. Nonetheless, it seems likely that patients discharged on warfarin alone or no outpatient therapy had already completed a course of UFH or LMWH therapy as inpatients, and were discharged after their INRs attained the desired therapeutic level.<sup>3</sup> In contrast, it is likely that patients treated with enoxaparin as outpatients started such therapy as inpatients but were discharged to home before they were ready to be maintained on oral warfarin therapy

**Table 7.** DVT Readmissions During 1 Year After Index Hospitalization

Anticoagulant Therapy After Discharge	Number of Patients	DVT Readmissions (%)	Cost Per Patient
Warfarin only	1696	153 (9.0)	\$715
Heparin only	13	3 (23.1)	\$1395
Enoxaparin/warfarin	164	11 (6.7)	\$575
Heparin/warfarin	16	3 (18.8)	\$778
No discharge therapy	1577	154 (9.8)	\$850

DVT = deep vein thrombosis.

alone. This possibility is also supported by the higher outpatient medical costs associated with enoxaparin/warfarin therapy primarily because of more frequent follow-up visits and laboratory tests in that cohort—services that might have been provided in the hospital had they stayed longer.

In conclusion, this study confirms previous research indicating that outpatient treatment of DVT with enoxaparin/warfarin therapy is not only feasible and safe but also reduces the cost of managing this serious disorder.

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