

# Are There Any Differences in the Clinical and Economic Outcomes Between US Cancer Patients Receiving Appropriate or Inappropriate Venous Thromboembolism Prophylaxis?

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## Abstract

**Purpose:** Despite evidence-based recommendations existing for the prevention of venous thromboembolism (VTE) in cancer patients, prophylaxis is often underused and inappropriately prescribed. This study compared the efficacy and cost of appropriate and partial prophylaxis in cancer patients at risk of VTE.

**Methods:** Discharge records for inpatients age  $\geq 40$  years, with a primary cancer diagnosis, and receiving some form of American College of Chest Physicians (ACCP) –recommended therapy in the Premier Perspective database (Premier Inc, Charlotte, NC; January 2002 to December 2006) were categorized into appropriate (in accordance with ACCP recommendations) or partial prophylaxis (inappropriate type, insufficient dose, or insufficient duration of prophylaxis) groups. VTE events, death, 30-day readmission, major and minor bleeds, and hospital costs were compared between groups using univariate and multivariate regression analysis.

**Results:** Of the 83,794 discharges included, only 16% received appropriate prophylaxis. Partial prophylaxis conferred a significantly increased risk in hospital-acquired VTE (odds ratio [OR], 3.09; 95% CI, 2.51 to 3.80;  $P < .001$ ), in-hospital death (OR, 1.48; 95% CI, 1.29 to 1.69;  $P < .001$ ), and 30-day VTE readmission (OR, 3.11; 95% CI, 1.54 to 6.26;  $P = .002$ ) compared with appropriate prophylaxis. No major bleeds were recorded in the database and no difference was observed in the rates of minor bleeding. The total cost per discharge was higher for partial prophylaxis (\$17,128) than appropriate prophylaxis (\$15,384), with an adjusted mean difference of \$1,275 in favor of appropriate prophylaxis.

**Conclusion:** In cancer patients at risk of VTE, appropriate prophylaxis reduced the hospital costs and incidence of VTE, mortality, and VTE readmission compared with partial prophylaxis. Increased appropriate use of ACCP recommendations may reduce the clinical and economic burden of VTE.

## Introduction

The risk of venous thromboembolism (VTE) is high in hospitalized patients with cancer.<sup>1-4</sup> In a study of more than 40 million cancer patients from 1979 through 1999, the incidence of VTE (pulmonary embolism [PE]) or deep-vein thrombosis [DVT]) was twice that of patients without cancer.<sup>4</sup> Furthermore, in a recent retrospective study of approximately 66,000 hospitalized neutropenic cancer patients, 5.4% of patients developed VTE during the 7-year study, and in-hospital mortality was significantly higher in patients with VTE (odds ratio [OR], 2.01; 95% CI, 1.83 to 2.22) compared with those without VTE.<sup>3</sup> Indeed, VTE is the second leading cause of death, after cancer, in cancer patients.<sup>5</sup>

VTE prophylaxis in cancer patients is associated with considerable clinical benefit. In a recent systemic review and meta-analysis of 11 anticoagulant studies in cancer patients, significantly lower overall 1-year mortality was demonstrated in patients receiving anticoagulation, with a relative risk of mortality of 0.88 (95% CI, 0.79 to 0.98;  $P = .015$ ) in patients receiving low-molecular-weight heparin.<sup>6</sup> To this end, evidence-based guidelines, such as those from American College of Chest Physicians (ACCP) and American Society of Clinical Oncology, provide recommendations on the best prophylaxis practices in cancer patients.<sup>7-9</sup> Furthermore, National Comprehensive Cancer Network guidelines recommend “prophylactic anticoagulation therapy for all in-patients with a diagnosis of active

cancer (or for whom clinical suspicion of cancer exists) who do not have a contraindication to such therapy.”<sup>10</sup>

Despite the wide availability of evidence-based guidelines, VTE prophylaxis remains underused in surgical and medical cancer patients.<sup>11,12</sup> A 4-year retrospective study in medically ill US patients reported that only 25% of cancer patients received prophylaxis.<sup>12</sup> This is consistent with the results from the FRONTLINE (Fundamental Research in Oncology and Thrombosis) survey of 3,891 clinicians, which reported that more than 50% of surgeons routinely used prophylaxis in surgical cancer patients, whereas medical oncologists provided prophylaxis to less than 5% of cancer patients.<sup>11</sup> Furthermore, the VTE prophylaxis provided to the majority of cancer patients often fails to meet the stringent criteria that have demonstrated benefit in clinical trials. ACCP guidelines outline the type and dose of medication, time of initiation of therapy and duration of prophylaxis. Appropriate prophylaxis is achieved only by providing the patient with the appropriate drug (or device), at the appropriate dose, and for the appropriate duration. In a recent study in US medical and surgical discharges, 56% of cancer patients received some form of prophylaxis, but only 28% received appropriate ACCP-recommended prophylaxis.<sup>13</sup>

Few studies have evaluated the true impact of failing to meet best-practice recommendations for prophylaxis in real-world cancer patients. This study assesses the efficacy and cost of

appropriate prophylaxis (defined as prophylaxis that adheres fully with ACCP recommendations) and partial prophylaxis (defined as prophylaxis with insufficient duration, inappropriate dose, or inappropriate type of VTE prophylaxis according to ACCP recommendations) in cancer patients who are at risk of VTE.

## Methods

### Data Collection

This study was a retrospective analysis of in-patient hospital discharge records between January 2002 and December 2006. The analysis used the Premier Perspective database, which contains information from approximately 5.5 million patient discharges per year across the United States, from not-for-profit, nongovernmental, community, and teaching hospitals and health systems. All patient records used in the study were de-identified in accordance with the Health Insurance Portability and Accountability Act 1996. Because of patient de-identification and because the study did not involve live human subjects, the study was exempt from institutional review board overview under the Common Rule, 45 CFR §46.001[b][4].

### Patient Selection

The methods for patient selection and assessment of appropriate prophylaxis were adapted from a previously reported study.<sup>13</sup> Discharge records were included if patients had a primary diagnosis of cancer; were at risk of VTE according to ACCP guidelines; and received some form of ACCP-recommended therapy. In addition, patients were included if they had a complete hospital stay of  $\geq 6$  days (to reflect a severely medically ill population)<sup>14</sup> and were not transferred from another acute care facility. Discharge records were excluded if patients had a potential contraindication to, or disease requiring modification of, ACCP-recommended anticoagulant therapy. Discharges with potential contraindications to VTE prophylaxis were excluded from the analysis. These contraindications were indicated by a secondary International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code that suggested the presence of active peptic ulcer disease, malignant hypertension, blood disease, human immunodeficiency virus, pregnancy, VTE present on admission, intubation of the gastrointestinal tract or respiratory tracts, liver disease, thrombocytopenia, or insufficient renal function (modified from McGarry et al<sup>15</sup>).

### Classification of Appropriate Versus Partial Prophylaxis

The discharge records were assessed to ascertain whether patients received VTE prophylaxis that was appropriate according to ACCP guidelines, with type, dosage, and duration of therapy considered. Discharge records were categorized into two groups, either appropriate or partial prophylaxis. In the appropriate prophylaxis group, discharges had to receive appropriate prophylaxis on the basis of the ACCP recommendations for the discharge's length of stay minus 2 days (to accommodate the

possibility of partial days of stay occurring at admission and discharge) plus a minimum of three days of preventative-level dosing to ensure that VTE prophylaxis has run its course and that the patient was not actively treated for VTE. In the partial prophylaxis group, discharges received a form of prophylaxis that was not in accordance with ACCP guidelines as a result of either insufficient duration or dosage of therapy or a mechanical device alone being prescribed when pharmacologic prophylaxis was recommended.

### Outcomes

The analysis compared clinical outcomes in the appropriate and partial prophylaxis groups; these were hospital-acquired VTE events (ie, DVT or PE that were developed during hospitalization and were not present on admission) and in-patient mortality. In addition, the rate of hospital readmission within 30 days was compared, both for readmission because of VTE and all-cause readmission. The overall length of stay in hospital and the length of stay in the intensive care unit (ICU) were also assessed; data are given as mean  $\pm$  standard deviation (SD). Regarding safety, the rate of major (principal or secondary ICD-9 code for bleeding and was transfused  $> 2$  units of packed RBCs) and minor bleeding (principal or secondary ICD-9 code for bleeding and was transfused  $\leq 2$  units of packed RBCs) was evaluated in both groups. Patients who received a transfusion on the day of, or the day before, a surgical procedure were not included in the adverse event for bleeding population. To assess the health economic consequences of appropriate versus partial prophylaxis, total and departmental hospital costs per discharge were estimated; expenditure from a number of different categories, such as anticoagulant costs, laboratory costs, and nursing costs were also compared.

### Analysis

*Univariate analysis.* Univariate analysis was performed to compare the individual variables between the groups. The variables compared were in-patient mortality, hospital-acquired VTE events, major and minor bleeding, and 30-day readmissions. Total and departmental hospital costs per discharge were also compared by univariate analyses. Results were considered statistically significant at a level of  $P < .05$ .

### Multivariate Regression Modeling

Multivariate regression modeling was performed to adjust for confounders between the appropriate and partial prophylaxis groups. The initial step was case-control matching between the two study cohorts (1:2 appropriate:partial prophylaxis) on the basis of the discharge's age group, gender, 3M All Patient Refined–Diagnosis Related Group Severity of Illness (APR-DRG SOI) subclass, surgery (yes/no), and the presence of other VTE risk factors (yes/no). The resulting appropriate prophylaxis and partial prophylaxis cohorts were used in a multivariate logistic regression model that included primary insurance payer, census region, hospital teaching status, urban versus rural population,

hospital bed number, and aspirin usage as covariates. Results were considered statistically significant at a level of  $P < .05$ .

## Results

A total of 83,794 discharge records were included in this analysis. Of these, only 13,387 (16.0%) discharges received appropriate prophylaxis, with the majority of patients (70,407 [84.0%]) receiving partial prophylaxis. A similar proportion of medical and surgical discharges received appropriate prophylaxis (15.8% *v* 16.2%) and partial prophylaxis groups (84.2% *v* 83.8%). The age of medical and surgical discharges was also similar in the appropriate prophylaxis (mean  $\pm$  SD, 64.0  $\pm$  12.9 years and 67.4  $\pm$  12.7 years, respectively) and partial prophylaxis groups (63.8  $\pm$  13.7 years and 67.4  $\pm$  13.4 years, respectively). Gender, type of payer, and age did not seem to influence the appropriateness of therapy, although statistical tests were not performed for the comparison (Table 1). Patients treated in smaller hospitals tended to be more likely to receive partial rather than appropriate prophylaxis.

## Clinical Outcomes

The rate of in-hospital VTE events was lower with appropriate prophylaxis than with partial prophylaxis (0.8% *v* 2.9%,  $P < .001$ ; Table 2). Mortality rates were also lower in the appropriate prophylaxis group (2.6% *v* 4.2%;  $P < .001$ ). A similar proportion of patients receiving appropriate and partial prophylaxis were readmitted within 30 days (2.1% and 1.9%, respectively;  $P = .134$ ); however, fewer patients receiving appropriate prophylaxis were readmitted for VTE (0.1% *v* 0.2%;  $P = .021$ ). The mean length of stay in hospital was shorter for patients receiving appropriate prophylaxis compared with partial prophylaxis (8.9  $\pm$  4.2 *v* 10.5  $\pm$  6.5 days, respectively;  $P < .001$ ). Similarly, the length of stay in the ICU was 2.7  $\pm$  3.0 days ( $P < .001$ ) in the appropriate prophylaxis group compared with 3.3  $\pm$  4.1 days ( $P < .001$ ) for patients receiving partial prophylaxis.

Following multivariate analysis, partial prophylaxis was an independent predictor of in-hospital VTE events (OR, 3.09; 95% CI, 2.51 to 3.80;  $P < .001$ ) or death (OR, 1.48; 95% CI, 1.29 to 1.69;  $P < .001$ ) when compared with appropriate prophylaxis (Table 3). Furthermore, the VTE readmission rate was significantly higher with partial prophylaxis than with appropriate prophylaxis (OR, 3.11; 95% CI, 1.54 to 6.26;  $P = .0015$ ). There was no significant difference between the groups in readmission for any cause.

In the safety analysis, the effect of appropriate adherence with ACCP guidelines on the OR for major bleeds could not be evaluated, as no major bleeds were recorded in either group. It is likely that the miscoding of bleeding in the discharge records contributed to this result. There was no significant difference in the rate of minor bleeding between groups (Table 3).

## Economic Outcomes

When the cost of VTE prevention was compared, the mean total cost per discharge was higher with partial prophylaxis

(\$17,128) than with appropriate prophylaxis (\$15,384; Table 4). Following adjustment via regression modeling for variables such as primary insurance payer, census region, and hospital teaching status, the mean estimated cost difference was \$1,275 per discharge in favor of appropriate prophylaxis. The largest costs associated with VTE management were facility costs for both appropriate and partial prophylaxis. Anticoagulant, pharmacy, and mechanical device costs were lower with partial prophylaxis than with appropriate prophylaxis ( $-\$4$  to  $-\$11$  per discharge) but imaging, facility, and ICU costs were substantially higher (\$250 to \$560 per discharge; Table 4).

## Discussion

This study demonstrates that appropriate prophylaxis, as defined by ACCP recommendations for prophylaxis type, dose, and duration, was used in only 16% of cancer patients considered to be at risk of VTE and receiving some form of prophylaxis. Partial prophylaxis was found to be an independent predictor for higher rates of in-hospital VTE events, mortality, and VTE readmissions compared with appropriate prophylaxis. As well as a reduction in clinical events with appropriate prophylaxis, an overall mean cost saving of \$1,275 per discharge was observed. The results of this study highlight the clinical and economic benefits of following ACCP guideline recommendations, with inappropriate use of prophylaxis potentially resulting in a missed opportunity to improve clinical outcomes and save health care resources.

This is the first study in cancer patients that assesses both the clinical and economic outcomes associated with ACCP-recommended VTE prophylaxis. Other large-scale studies of prophylaxis rates included all surgical or medical patients,<sup>16</sup> or reported rates of any form of prophylaxis.<sup>12</sup> Reporting rates and outcomes after any form of prophylaxis may give the impression of an artificially inflated level of prophylaxis prescribing and may potentially lead to an underestimation of the clinical value of VTE prophylaxis.

The effects of changing the type and duration of prophylaxis on VTE incidence was investigated in patients undergoing curative or pelvic surgery for cancer in the ENOXACAN (Enoxaparin and Cancer) I and II trials.<sup>17,18</sup> In ENOXACAN I ( $n = 631$ ), the incidence of VTE after surgery was 14.7% with enoxaparin (40 mg once daily for 10 days) versus 18.2% in patients who received low-dose unfractionated heparin (three times daily).<sup>17</sup> In the ENOXACAN II trial, patients undergoing major abdominal surgery for cancer received enoxaparin once daily for 6 to 10 days after surgery, then either enoxaparin ( $n = 165$ ) or placebo ( $n = 167$ ) for another 21 days. Long-term treatment with enoxaparin led to a significantly lower incidence of VTE compared with placebo (4.8% and 12.0%, respectively;  $P = .02$ ).<sup>18</sup> These studies provide valuable information regarding appropriate prophylaxis in cancer patients; however, clinical trials have a highly selected population and adherence to protocol is high. This study provides data on outcomes following

**Table 1. Patient Demographics and Clinical Characteristics**

Variable	Appropriate Prophylaxis (%) <sup>*</sup>			Partial Prophylaxis (%) <sup>†</sup>		
	All	Medical	Surgical	All	Medical	Surgical
Sex						
Female	47.4	20.7	26.8	45.7	20.3	25.4
Male	52.6	27.0	25.6	54.3	28.1	26.2
Payer						
Indemnity	7.3	4.0	3.4	7.3	4.1	3.2
Managed care	30.2	17.0	13.2	27.2	15.7	11.5
Medicaid	5.6	2.3	3.4	5.8	2.5	3.4
Medicare	53.1	22.4	30.7	54.6	23.4	31.2
Other	3.8	2.1	1.7	5.0	2.6	2.4
APR-DRG SOI						
1	18.9	11.4	7.4	16.0	10.5	5.4
2	50.2	26.0	24.2	46.4	24.9	21.6
3	28.3	9.6	18.6	32.8	11.5	21.3
4	2.8	0.6	2.1	4.9	1.5	3.4
No. of beds						
6-200	4.9	2.7	2.2	8.9	4.6	4.3
201-499	41.6	18.9	22.7	48.2	23.3	24.9
≥ 500	53.6	26.1	27.4	42.9	20.5	22.4
Location						
Rural	7.5	3.9	3.6	9.5	4.7	4.8
Urban	92.5	43.8	48.7	90.5	43.7	46.8
Age, years						
< 40	3.0	1.8	1.2	3.5	2.1	1.4
40-64	40.1	21.5	18.5	39.6	21.4	18.2
65-74	29.0	13.1	15.9	28.4	13.5	14.9
≥ 75	28.0	11.3	16.8	28.5	11.3	17.2
Region						
Midwest	21.0	8.3	12.7	17.1	8.1	8.9
Northeast	32.4	14.7	17.7	16.3	6.9	9.5
South	38.8	20.8	18.0	55.8	27.4	28.4
West	7.9	3.9	4.0	10.9	6.0	4.9

Abbreviation: APR-DRG SOI, All Patient Refined–Diagnosis Related Group Severity of Illness score.

\*n = 13,387.

†n = 70,407.

prophylaxis (both appropriate and partial) in a large population of patients seen in real-world clinical practice.

In a previous study, we evaluated whether prophylaxis was appropriate in seven groups with different acute medical conditions, including cancer (n = 30,708).<sup>13</sup> Appropriate prophylaxis was received by 34% of all medical patients investigated, including only 28% of at-risk cancer patients. When the rate of appropriate prophylaxis prescribed by different clinical specialists was investigated, only 25% of attend-

ing medical oncologists were found to prescribe guideline-adherent prophylaxis, compared with 42% of cardiologists and 37% of surgeons. Increased education of oncologists may help to raise awareness and lead to better implementation of guidelines. Furthermore, in a systematic review of 30 studies investigating strategies to optimize VTE prophylaxis practices in hospitals, the use of a number of integrated active approaches was more effective than a single strategy used alone.<sup>19</sup> Clinical-decision support systems were among the most effective strategies for improving prescribing prac-

**Table 2. Proportion of Patients Experiencing Efficacy and Safety Outcomes With Appropriate or Partial Prophylaxis**

Outcome	Appropriate Prophylaxis (%) <sup>*</sup>		Partial Prophylaxis (%) <sup>†</sup>	
	No.	%	No.	%
VTE event	107	0.80	2,033	2.89
Mortality	344	2.57	2,979	4.23
All readmissions	311	2.32	1,777	2.52
VTE readmissions	12	0.09	182	0.26
Major bleeding <sup>‡</sup>	0	0	0	0
Minor bleeding	18	0.13	194	0.28

Abbreviation: VTE, venous thromboembolism.

<sup>\*</sup>n = 13,387.

<sup>†</sup>n = 70,407.

<sup>‡</sup>The lack of major bleeds observed in this study is likely the result of the miscoding of such events.

**Table 3. Odds Ratios for Efficacy and Safety Outcomes With Partial Versus Appropriate Prophylaxis**

Variable	Odds Ratio	95% CI	P
VTE events	3.09	2.51 to 3.80	< .001
Mortality	1.48	1.29 to 1.69	< .001
All readmissions	0.95	0.81 to 1.12	ns
VTE readmissions	3.11	1.54 to 6.26	< .01
Minor bleeding	1.62	0.94 to 2.78	ns

NOTE: Odds ratios are derived from multivariate regression analysis (Methods).

Abbreviations: VTE, venous thromboembolism; ns, not significant.

**Table 4. Cost Analysis of Appropriate and Partial Prophylaxis**

Cost Variable	Crude Cost per Discharge (dollars)				Estimated Difference (dollars) <sup>*</sup>
	Appropriate Prophylaxis		Partial Prophylaxis		
	Mean	SD	Mean	SD	
Total	15,384	10,283	17,128	13,832	1,275
Drug	1,370	1,769	1,857	3,168	105
Anticoagulants	107	152	142	291	-10
Facility	7,553	4,893	8,400	6,832	560
ICU	3,625	4,894	3,891	5,903	337
Laboratory	405	394	531	634	71
Nursing	849	2,159	1,252	3,457	0
Imaging	599	755	780	987	251
Pharmacy	108	152	143	291	-11
Mechanical prophylaxis	115	185	113	192	-4

Abbreviations: SD, standard deviation; ICU, intensive care unit.

<sup>\*</sup>Estimated difference based on the modeling coefficients to allow for demographic and clinical demographics of the groups.

tice; this may be because such systems minimized errors made by individual clinicians with varying knowledge of VTE prevention.

As the current analysis was based on retrospective discharge records, the individual circumstances that may have led physicians not to adopt practices in line with current guidelines can not be fully evaluated. The study may also be limited by the use

of the Premier Perspective database; although this database contains information from a large number of hospitals across the US, it is possible that it may not be representative of the entire US population of hospitalized cancer patients. The application of inclusion and exclusion criteria regarding concomitant clinical conditions and length of stay may also have influenced the results by selecting a population that was not at the same risk level as the general population. Regarding the safety analysis,

the use of ICD-9 codes could have contributed to the absence of major bleeds in this study. As bleeding is often miscoded, not coded, or coded as “common complications,” major bleeds may have occurred but were missed in this analysis.

To conclude, this study highlights the current underuse of appropriate prophylaxis in cancer patients at risk of VTE. Providing appropriate ACCP-recommended VTE prophylaxis was more effective for the prevention of clinical events and was associated with reduced expenditure of health care resources compared with partial prophylaxis. It is important that individual hospitals improve the use of appropriate prophylaxis to reduce both the clinical and economic burden posed by VTE.

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#### Authors' Disclosures of Potential Conflicts of Interest

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