Brief Report

Pulmonary Embolism Inpatients Treated With Rivaroxaban Had Shorter Hospital Stays and Lower Costs Compared With Warfarin

Jay M. Margolis, PharmD[1]; Steven Deitelzweig, MD[2]; Jeffrey Kline, MD[3]; Oth Tran, MA[4]; David M. Smith, PhD[4]; Concetta Crivera, PharmD[5]; Brahim Bookhart, MBA[5]; and Jeff Schein, DrPH[5]

[1]Truven Health Analytics, Bala Cynwyd, Pennsylvania; [2]Ochsner Health System and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, Louisiana; [3]Carolinas Medical Center, Indianapolis, Indiana; [4]Truven Health Analytics, Bethesda, Maryland; and [5]Janssen Scientific Affairs LLC, Raritan, New Jersey

ABSTRACT

Purpose: Using real-world data, this study compares inpatient length of stay (LOS) and costs for patients with a primary diagnosis of pulmonary embolism (PE) initiating treatment with oral anticoagulation with rivaroxaban versus warfarin.

Methods: Hospitalizations from MarketScan's Hospital Drug Database were selected from November 1, 2012, through December 31, 2013, for adults with a primary diagnosis of PE initiating treatment with rivaroxaban or warfarin. Warfarin patients were matched 1:1 to rivaroxaban patients using exact and propensity score matching. Hospital LOS, treatment patterns, and hospitalization costs were evaluated.

Findings: Matched cohorts included 751 rivaroxaban-treated patients and 751 warfarin-treated patients. Adjusted mean LOS was 3.77 days for rivaroxaban patients (95% CI, 3.66–3.87 days) and 5.48 days for warfarin patients (95% CI, 5.33–5.63 days; $P < .001$). Mean (SD) LOS was shorter for patients taking rivaroxaban whether admission was for provoked PE (rivaroxaban: 5.2 [5.1] days; warfarin: 7.0 [6.5] days; $P < .001$) or unprovoked PE (rivaroxaban: 3.4 [2.3] days; warfarin: 5.1 [2.7] days; $P < .001$). Mean (SD) days from first dose to discharge were 2.5 (1.7) (rivaroxaban) and 4.0 (2.9) (warfarin) when initiated with parenteral anticoagulants ($P < .001$) and 2.7 (1.7) (rivaroxaban) and 4.0 (2.2) (warfarin) without parenteral anticoagulants ($P < .001$). The rivaroxaban cohort incurred significantly lower unadjusted mean (SD) hospitalization costs (rivaroxaban: $8473 [$9105]; warfarin: $10,291 [$9185]; $P < .001$), confirmed by covariate adjustment with generalized linear modeling estimating predicted mean hospitalization costs of $8266 for rivaroxaban patients (95% CI, $7851–$8681) and $10,511 for warfarin patients (95% CI, $10,031–$10,992; $P < .001$).

Implications: patients with PE treated with rivaroxaban incurred significantly lower hospitalization costs by $2245 per admission compared with patients treated with warfarin, which was attributable to cost offsets from 1.71 fewer days of stay in the hospital. (*Clin Ther*. 2016;38:2496–2503) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: hospitalization costs, length of stay, pulmonary embolism, rivaroxaban, warfarin.

INTRODUCTION

Pulmonary embolism (PE) is a common and sometimes fatal form of venous thromboembolism (VTE). An estimated 650,000 individuals are affected in the United States each year, with approximately 20% to 25% mortality within the first day of diagnosis and >10% at mortal risk during the first month after diagnosis, imposing a substantial economic burden on

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the US health care system, with estimated annual costs exceeding $1.5 billion.[1–3]

Clinical practice treatment guidelines recommend short-term treatment with parenteral anticoagulants, such as low-molecular-weight heparin, fondaparinux, or unfractionated heparin, either alone or with an oral vitamin K antagonist (VKA).[4] Use of VKA anticoagulants, most commonly warfarin, typically start concurrently with or shortly after initiating heparin therapy. Despite proven efficacy of VKA anticoagulants in preventing recurrence, they have several clinical limitations. Their onset of action can take several days, they have numerous chemical interactions, and their narrow therapeutic range requires regular laboratory monitoring for anticoagulation optimization.[5–7]

Alternatives to VKAs for oral anticoagulant therapy available in the United States include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban, apixaban, and edoxaban. They exhibit a quicker onset of action, have fewer food and drug interactions, and do not require routine laboratory monitoring.[8]

Rivaroxaban is an oral inhibitor of factor Xa, with onset of action 2 to 4 hours after initiation and no requirement for coagulation monitoring.[9] Post hoc analyses of the EINSTEIN clinical trials revealed equivalent efficacy and significantly shorter hospital stays, with mean reductions in stay of 1.6 days in rivaroxaban-treated patients with VTE and 1.7 days for rivaroxaban-treated patients with PE than those with standard-of-care treatment.[10,11] Little is known in real-world clinical practice about the length of hospital stay and economic burden attributable to hospitalization in patients with PE initiating treatment with inpatient oral anticoagulation with rivaroxaban versus VKAs.

The primary objective of this study was to augment the information learned in the clinical trial setting by examining hospital length of stay (LOS), treatment patterns, and hospitalization costs in real-world practice using a data set derived from a large and geographically diverse sample of US hospitals, comparing patients hospitalized with a primary PE diagnosis who were receiving rivaroxaban versus warfarin oral anticoagulation therapy during their hospital stay. This brief report is a subset analysis of a larger VTE study that focused on matched cohorts of 751 patient admissions with a primary diagnosis of PE.

METHODS

The data source was completed admission records from the Truven Health MarketScan Hospital Drug Database (HDD) from November 1, 2012, through December 31, 2013, including inpatient diagnoses, procedures, and drugs administered, derived from the ordering and billing systems of >600 geographically and demographically diverse US hospitals. This study used only deidentified patient records in full compliance with the Health Insurance Portability and Accountability Act of 1996. Because it did not involve collection, use, or transmittal of individually identifiable data, institutional review board approval to conduct this study was not required.

Completed admissions with a primary diagnosis of PE (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] diagnosis code 415.1x) were selected from the HDD from November 1, 2012, through December 31, 2013, for adults receiving rivaroxaban or warfarin during hospitalization. Low-molecular-weight heparin or unfractionated heparin therapy may have been received before patients received rivaroxaban or warfarin. Patients were excluded from analysis if a hospital admission record was found within 12 months before the index date with a VTE diagnosis in any position to increase the likelihood of our admissions focusing on a patient's initial PE event. Hospitalizations were also excluded for patients receiving both rivaroxaban and warfarin, those receiving either apixaban or dabigatran etexilate mesylate (edoxaban was not yet available in the United States), patients <18 years old, and those who were pregnant.

Patients receiving warfarin were matched 1:1 to patients receiving rivaroxaban using a combination of exact matching on the primary PE diagnoses followed by propensity score matching using a logistic regression model to predict the probability of initiating rivaroxaban treatment. The independent variables included patient demographic characteristics (age, sex, payer, admission year, admission source, admission to intensive care unit), hospital demographic characteristics (geographic location, teaching, urban, bed size), comorbidity index, and clinical characteristics reflecting specific baseline comorbidities (anemia, arrhythmia, cancer, chronic obstructive pulmonary disease, diabetes, drug abuse, dyslipidemia, esophageal disorders, heart failure, hypertension,

hypothyroidism, ischemic heart disease, obesity, renal disease). The balance achieved in the matching procedure was assessed by the standardized mean differences of the covariates in the logistic regression model. A covariate was considered balanced between cohorts if the standardized mean difference was not >10%.[12,13]

Hospital LOS (days from admission to discharge), days from admission to first dose, days from first dose to discharge, and hospitalization costs by service categories, including room costs, inpatient medication costs, laboratory tests, procedures, and other services, were reported. LOS results were further stratified into provoked PE versus unprovoked PE, with provoked PE defined as patients with a fracture diagnosis, a major surgical procedure, selected drugs (oral contraceptives, estrogens, progestins, selective estrogen receptor modulators, aromatase inhibitors, or erythropoiesis-stimulating agents), a postpartum diagnosis, or a malignant neoplasm diagnosis.[4] Costs for all inpatient hospital services were reported, categorized according to room costs, inpatient medications, laboratory tests, procedures, all other inpatient services (eg, imaging, respiratory therapy, other therapy, medical or surgical services, medical or surgical supplies, operating room, other), and total. Hospital costs were calculated by applying the Centers for Medicare & Medicaid Services ratios of costs to charges at both the hospital and department levels and adjusted to 2015 US dollars using the Medical Care Component of the Consumer Price Index. Baseline demographic and clinical characteristics, including selected comorbidities and concomitant medications, were also recorded.

Dependent and independent variables were summarized descriptively, with observed differences between treatment groups tested using χ^2 tests for categorical variables and t tests for continuous variables. Generalized linear models (GLMs) were fitted to the main outcomes of LOS (negative binomial, log link regression), days from first dose to discharge (negative binomial, log link regression), and hospitalization costs (log link function and γ error distribution), adjusting for demographic and clinical characteristics. $P < .05$ was set as the threshold for statistically significant differences. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

From an initial sampling of 22,781 patients admitted with a primary diagnosis of VTE, 22,009 patients lacked a prior VTE hospitalization, including 1879 patients treated with rivaroxaban and 16,557 treated with warfarin. Application of the remaining selection criteria yielded a final cohort of 751 patients treated with rivaroxaban with a primary diagnosis of PE and subsequently matched 1:1 with patients treated with warfarin, producing final matched cohorts, each including 751 patients with primary PE. The 2 treatment cohorts were well balanced for demographic and clinical characteristics after matching (Table).

Patients with primary PE treated with rivaroxaban had significantly shorter observed mean (SD) LOS than patients treated with warfarin (rivaroxaban patients: 3.8 [3.2] days; warfarin patients: 5.4 [3.9] days; $P < .001$) (Figure 1). GLM modeling of LOS, adjusting for demographic and clinical characteristics, confirmed these results, with an adjusted overall mean LOS for PE of 3.77 days (95% CI, 3.66–3.87 days) for rivaroxaban and 5.48 days (95% CI, 5.33–5.63 days) for warfarin for an adjusted difference of 1.71 fewer days per admission for the rivaroxaban cohort ($P < .001$). We further observed that the rivaroxaban cohort had significantly shorter mean LOS than the warfarin cohort whether the PE was considered provoked (rivaroxaban: 5.2 [5.1] days; warfarin: 7.0 [6.5] days; $P < .001$) or unprovoked (rivaroxaban: 3.4 [2.3] days; warfarin: 5.1 [2.7] days; $P < .001$) (Figure 1).

The proportion of patients initiating treatment with parenteral anticoagulants was 66% in both treatment cohorts; however, the observed mean (SD) time from admission to first treatment dose was generally longer for patients treated with rivaroxaban (with parenteral anticoagulants: rivaroxaban: 2.2 [1.7] days; warfarin: 1.8 [1.8] days; $P < .001$; without parenteral anticoagulants: rivaroxaban: 1.0 [1.6] days; warfarin: 0.4 [0.7] days; $P < .001$). The observed mean (SD) time from first treatment dose to discharge was significantly shorter for rivaroxaban-treated compared with warfarin-treated patients regardless of treatment with or without parenteral anticoagulants (with parenteral anticoagulants: rivaroxaban: 2.5 [1.7] days; warfarin: 4.0 [2.9] days; $P < .001$; without parenteral anticoagulants: rivaroxaban: 2.7 [1.7] days; warfarin: 4.0 [2.2] days; $P < .001$). A similar pattern was observed

Table. Patient and hospital characteristics of hospitalized patients with pulmonary embolism treated with rivaroxaban versus warfarin: final study cohorts meeting all selection criteria and propensity score matching*

Characteristic	Rivaroxaban (n = 751)	Warfarin (n = 751)	*P*
Age, mean (SD), y	63.6 (16.5)	63.9 (16.7)	0.788
Age group			0.363
18-24 y	0.9	1.6	
25-34 y	4.8	4.3	
35-44 y	8.3	8.9	
45-54 y	16.0	12.4	
55-64 y	17.2	19.0	
65-74 y	23.6	22.5	
≥75 y	29.3	31.3	
Sex			0.836
Male	47.9	47.4	
Female	52.1	52.6	
Principal payer			0.709
Private insurance	35.0	37.4	
Medicare	54.7	54.3	
Medicaid	4.1	3.3	
Other	6.1	4.9	
Hospital type			0.946
Teaching	17.2	17.3	
Nonteaching	82.8	82.7	
Hospital setting			>0.99
Urban	86.6	86.6	
Rural	13.4	13.4	
Licensed bed size			0.740
1-199 beds	22.9	23.4	
200-299 beds	18.1	19.0	
300-499 beds	28.1	25.6	
≥500 beds	30.9	32.0	
Discharge status			0.078
Home/home health	88.0	86.7	
Transferred	10.9	13.0	
Other	1.1	0.3	
No. of diagnoses, mean (SD)†	9.8 (4.6)	10.0 (4.5)	0.464
Comorbid conditions‡			
Hypertension	61.1	62.3	0.633
Dyslipidemia	39.0	40.5	0.562
Ischemic heart disease or angina	21.6	20.9	0.752
COPD	21.2	21.3	0.950
Cardiac arrhythmia	20.5	21.0	0.799
Diseases of the esophagus	19.7	20.5	0.699
Diabetes	19.6	18.1	0.468
Anemia	18.6	20.1	0.473

(continued)

Table. (continued).

Characteristic	Rivaroxaban (n = 751)	Warfarin (n = 751)	*P*
Overweight or obese	18.2	21.6	0.106
Renal disease	14.5	15.0	0.771
Nondependent abuse of drugs	13.8	13.7	0.940
Acquired hypothyroidism	13.0	10.9	0.204
Heart failure	12.1	11.5	0.689
Malignant cancer	8.9	8.7	0.855
Cardiometabolic medications			
β-blockers	39.9	41.5	0.529
Antiplatelets	38.9	41.1	0.371
Statins	35.0	36.1	0.666
Diuretics	28.6	34.8	0.011
ACE inhibitors	27.3	27.2	0.954
Calcium channel blockers	22.5	22.2	0.901
ARBs	10.3	10.7	0.800
Thrombolytics	9.1	13.7	0.004

ARBs = angiotensin II receptor blockers; COPD= chronic obstructive pulmonary disease; PE = pulmonary embolism.
*Data are presented as percentage of patients unless otherwise indicated.
†Unique 3-digit International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.
‡Comorbid conditions reported in <5% of these admissions included peripheral vascular disease, cerebrovascular disease, hepatic disease, major bleed, abdominal surgery, orthopedic surgery, and inflammatory bowel disease.

in comparing provoked and unprovoked PE treatment cohorts. Modeling mean time from first dose to discharge confirmed the observed overall results with 2.57 days (95% CI, 2.53–2.61 days) for rivaroxaban and 4.01 days (95% CI, 3.95–4.08 days) for warfarin for an adjusted mean difference of 1.44 fewer days for rivaroxaban-treated patients ($P < .001$).

The rivaroxaban cohort had significantly lower observed total mean (SD) hospitalization costs ($8473 [$9105] vs $10,291 [$9185]; $P < .001$) and room charges ($2162 [$2556] vs $3239 [$3182]; $P < .001$) (Figure 2). Overall mean (SD) inpatient medication costs were not statistically different between treatment groups (rivaroxaban: $679 [$1554]; warfarin: $800 [$1313]; $P = 0.101$) despite higher oral anticoagulant cost for rivaroxaban-treated patients (rivaroxaban: $22 [$29]; warfarin: $5 [$9]; $P < .001$). Other inpatient costs for rivaroxaban-treated and warfarin-treated patients included laboratory tests (rivaroxaban: $444 [$600]; warfarin: $534 [$485]; $P = .001$), procedures (rivaroxaban: $249 [$1239]; warfarin: $156 [$626]; $P = 0.068$), and other inpatient services (rivaroxaban: $4881 [$5298]; warfarin: $5400 [$4759]; $P = 0.046$). (Component mean costs add to less than the total mean hospitalization costs attributable to ratios of costs to charges rounding.) GLM modeling results for total hospital costs, adjusting for demographic and clinical characteristics, confirmed the statistically significant differences in mean costs between the matched rivaroxaban and warfarin cohorts. Predicted mean total hospitalization costs for the rivaroxaban cohort were $8266 (95% CI, $7851–$8681; median, $6515) and $10,511 (95% CI, $10,031–$10,992; median, $8721) for warfarin-treated patients, a significant adjusted mean difference of $2245 between cohorts per admission.

DISCUSSION

This study found that admissions for treatment of PE were significantly shorter by 1.71 days, with fewer days from first dose to discharge, and had significantly

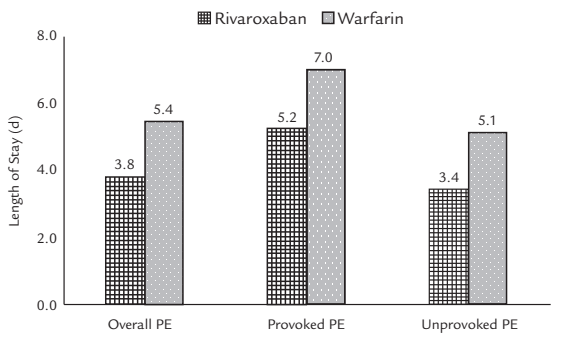

Figure 1. Observed mean lengths of hospital stay for the overall pulmonary embolism (PE) cohort, patients with provoked PE, and patients with unprovoked PE. All observed rivaroxaban versus warfarin comparisons were significant at $P < .001$.

lower mean hospitalization costs by $2245 when initiating treatment with oral anticoagulation with rivaroxaban compared with warfarin. The reduction in LOS was consistent across the provoked and unprovoked PE patient strata. This difference, found in real-world primary PE hospitalizations, closely aligns with the EINSTEIN clinical trials.[10,11] The subanalysis of North American EINSTEIN patients found rivaroxaban-treated patients with PE experienced a mean reduction of 1.7 days compared with enoxaparin- and VKA-treated patients (mean LOS, 4.5 days for the rivaroxaban-treated patients vs 6.2 days for the enoxaparin- and VKA-treated patients; median, 3 vs 4 days; $P < .001$).[11] The results of the present study (3.77 vs 5.48 days for the rivaroxaban vs warfarin groups; median, 3.38 vs 4.99; $P < .001$) are important in that they corroborate the clinical trial findings in real-world clinical practices across a large sample of US hospitals.

The lower LOS with initiation of rivaroxaban treatment (compared with warfarin treatment) may account for the rivaroxaban cohort's significantly lower observed total mean hospitalization costs and room charges ($2162 vs $3239; $P < .001$). The predicted mean LOS and total hospitalization costs per admission (rivaroxaban: mean LOS, 3.77 days; mean costs, $8266; warfarin: mean LOS, 5.48 days;

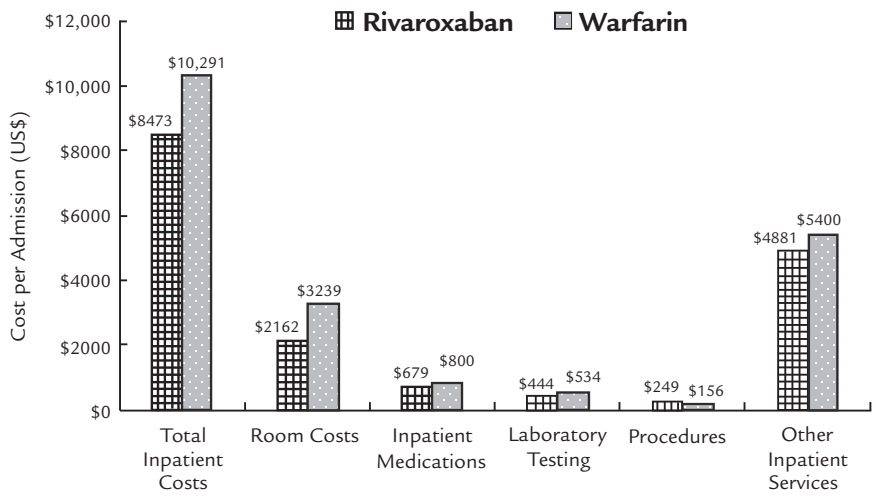

Figure 2. Mean costs per admission categorized by total inpatient costs, room costs, inpatient medications, laboratory costs, procedures, and other inpatient services in patients with pulmonary embolism treated with rivaroxaban or warfarin. Rivaroxaban versus warfarin cohort differences were significant at $P < .001$ for total inpatient costs, room costs, and laboratory testing and at $P = 0.046$ for other inpatients services. Differences were not statistically significant for inpatient medications at $P = 0.101$ and procedures at $P = 0.068$. Component costs add to less than total inpatient costs because of ratios of costs to charges rounding.

mean costs, $10,511) are well within the range reported by the 2012 weighted national averages from the Healthcare Cost and Utilization Project National Inpatient Sample report (mean LOS, 5.1 days; mean costs, $10,819 per admission) and a recent study of costs for patients with PE at Brigham and Women's Hospital (mean [SD] LOS, 4.1 [3.2] days; mean [SD] costs, $8764 [$7236] per admission).[14,15] A recent publication by Dasta et al[16] reported a mean total cost of hospitalization for PE of $9407 and a mean daily cost of $1735. Our finding of an estimated $2245 savings for rivaroxaban-treated patients and overall hospitalization costs are consistent with this finding. Two recent observational studies[17,18] with primary end points of LOS corroborated lower LOS for rivaroxaban-treated patients compared with warfarin-treated patients, including one study by Roberts et al[17] of patients with a discharge diagnosis of PE (January 2012 through March 2015) reporting median LOS of 2.7 days fewer for rivaroxaban-treated patients (N = 76) compared with patients treated with warfarin plus enoxaparin (N = 82) and a second study by Desai et al[18] of VTE-treated patients (N = 414) at one institution with significantly shorter LOS for rivaroxaban than those discharged with a warfarin prescription (3.5 vs 7.0 days, $P < .001$). Cohort sizes in these studies were substantially smaller than the present study and not geographically diverse, which may contribute to differences in findings.

These results provide valuable real-world estimates of hospital utilization and costs among patients with PE; however, the data source has limitations that should be noted. The HDD relies on hospital discharge records that may have inaccuracies in coding, billing, or missing data that could result in measurement error. All data used in this analysis, including propensity score matching, were limited to those found during the patient's hospitalization. Clinical history before and after hospitalization (eg, prior medication exposures, such as rivaroxaban or warfarin, before admission, preadmission comorbidity) was unavailable. Bias attributable to unknown or unmeasured covariates cannot be ruled out, especially because sociodemographic factors (eg, race, socioeconomic status, behaviors such as smoking) were unavailable. Finally, the HDD is a convenience sample of contributing US hospitals and, although large, may not represent the entire US population.

CONCLUSIONS

In summary, this real-world observational study of hospital admissions with a primary diagnosis of PE found that patients initiating oral anticoagulation therapy with rivaroxaban incurred significantly lower hospitalization costs by $2245 per admission compared with those initiating warfarin, attributable to the cost offset from 1.71 fewer days of stay in the hospital.

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CONFLICTS OF INTEREST

J.M. Margolis, O. Tran, and D.M. Smith are employees of Truven Health Analytics, which was paid by Janssen Scientific Affairs in connection with the development of this article. C. Crivera, B. Bookhart, and J. Schein are employees of Janssen Scientific Affairs. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Address correspondence to: Jay Margolis, PharmD, Truven Health Analytics, 332 Bryn Mawr Ave, Bala Cynwyd, PA 19004. E-mail: jay.margolis@truvenhealth.com