Effectiveness and Safety of Rivaroxaban in Patients With Cancer-Associated Venous Thrombosis

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Abstract

Background: Although not designated as guideline-recommended first-line anticoagulation therapy, patients are receiving rivaroxaban for the treatment and secondary prevention of cancer-associated venous thrombosis (CAT). We sought to estimate the cumulative incidence of recurrent venous thromboembolism (VTE), major bleeding, and mortality/hospice care in patients with CAT treated with outpatient rivaroxaban in routine practice. **Methods:** Using US MarketScan claims data from January 2012 through June 2015, we identified adults with active cancer (using SEER program coding) who had ≥ 1 primary hospitalization or emergency department discharge diagnosis code for VTE (index event) and received rivaroxaban as their first outpatient anticoagulant within 30 days of the index VTE. Patients were required to have ≥ 180 days of continuous medical/prescription benefits prior to the index VTE. Patients with a previous claim for VTE, atrial fibrillation, or valvular disease or receiving anticoagulation during the baseline period were excluded. We estimated the cumulative incidence with 95% CIs of recurrent VTE, major bleeding, and mortality or need for hospice care at 180 days, assuming competing risks. **Results:** A total of 949 patients with active cancer were initiated on rivaroxaban following their index VTE. Time from active cancer diagnosis to index CAT was ≤ 90 days for 27% of patients, 91 to 180 days for 19%, and >180 days for 54%. The mean [SD] age of patients was 62.5 [12.8] years, 43.6% had pulmonary embolism, and metastatic disease was present in 42.6%. During follow-up, there were 37 cases of recurrent VTE, 22 cases of major bleeding (17 gastrointestinal, 3 intracranial, 1 genitourinary, and 1 other bleed), and 105 deaths/hospice claims. The cumulative incidence estimate was 4.0% (95% CI, 2.8%–5.4%) for recurrent VTE, 2.7% (95% CI, 1.7%–4.0%) for major bleeding, and 11.3% (95% CI, 9.2%–13.6%) for mortality/hospice care. **Conclusions:** Event rates observed in this rivaroxaban-treated cohort were overall consistent with previous studies of patients with rivaroxaban- and warfarin-managed CAT.

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Patients with active cancer have up to a 7-fold increased risk of venous thromboembolism (VTE) compared with age-matched controls, corresponding to an

annual incidence of approximately 1 thrombotic event per 200 patients with active cancer.^{1–3} Although anticoagulation is the cornerstone of management of cancer-

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associated venous thrombosis (CAT), its use is complicated by patients' higher risk of both recurrent VTE and bleeding complications.^{3,4}

Randomized controlled trials (RCTs) have demonstrated superior efficacy of continued low-molecular-weight heparins (LMWHs) over parenteral bridging to vitamin K antagonist (VKA) therapy for treatment and secondary prevention of CAT.⁵⁻⁷ Consequently, current CAT treatment guidelines recommend LMWHs as first-line therapy, with oral anticoagulants reserved for patients unable or willing to use long-term parenteral agents.⁷⁻¹¹ Despite CAT guideline recommendations, nearly one-fifth of patients receive rivaroxaban for acute treatment and secondary prevention of CAT in routine clinical practice.¹²

This claims database analysis sought to estimate the cumulative incidence of recurrent VTE, major bleeding, and mortality/hospice care in patients with CAT treated with rivaroxaban.

Methods

This article was written in compliance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statement.¹³ We performed a retrospective, single-arm, administrative claims data–based analysis of patients with CAT treated with rivaroxaban as outpatients. Health insurance claims starting November 2012 (when rivaroxaban was approved for VTE treatment in the United States) through September 2015 (most recent data available at time of analysis) captured in the US Truven Health Analytics MarketScan Databases were used to perform this analysis. MarketScan combines 2 separate databases—a commercial and a Medicare supplemental database—to cover all age groups, and as of March 2017 contained claims from 260 contributing employers, 40 contributing health plans, and government and public organizations representing nearly 240 million covered American lives.¹⁴ MarketScan captures health plan enrollment records, demographics, ICD-9-CM diagnosis codes, procedure codes, admission and discharge dates, inpatient mortality data, outpatient medical services data, and prescription dispensing records. All data included in the MarketScan databases are deidentified and in compliance with the Health Insurance Portability and Accountability Act of 1996 to pre-

serve participant anonymity and confidentiality. For this reason, the study was deemed exempt from Institutional Review Board oversight.

To be included in the current analysis, patients aged ≥ 18 years had to have active cancer; ≥ 1 primary discharge diagnosis code for deep vein thrombosis (DVT; ICD-9-CM codes 451.1, 451.2, 453.40, 453.41, 453.42, 453.8, or 453.9) or pulmonary embolism (ICD-9-CM codes 415.1x); a positive predictive value for identifying any VTE of 95% (95% CI, 93–97)¹⁵ linked to a hospital or emergency department stay; and be newly initiated on rivaroxaban within 30 days of hospitalization or emergency department visit for the index VTE event. Patients were required to be continuously enrolled in their health plan, with medical and pharmacy benefits for at least 180 days prior to the index event date (which serves as the study's baseline period). Patients with a VTE, atrial fibrillation, or valvular heart disease claim or a prescription claim for any anticoagulant during this baseline period were excluded. Patients with active cancer were identified using the NCI/Cancer Research Network algorithm, which uses ICD-9-CM diagnosis, Current Procedural Technology codes, Diagnosis-Related Group classification system, Healthcare Common Procedure Coding System codes, and National Drug Codes.¹⁶

Primary end points for this study were recurrent VTE (identified by the presence of an ICD-9-CM code, as detailed in the previous paragraph, in the primary discharge code associated with a subsequent hospital admission), major bleeding (defined as bleeding-related hospitalizations per the Cunningham algorithm),¹⁷ and all-cause mortality or a claim for hospice care in the 180 days following the index VTE event. Although in-hospital mortality data are reported in the MarketScan databases, out-of-hospital mortality data are not. For this study, we combined in-hospital death and need for hospice care without subsequent healthcare claims into a single end point. A similar approach was previously shown in claims data to have a positive predictive value of approximately 93%¹⁸ for mortality, and is further supported by Mantha et al,¹⁹ who found that more than three-quarters of deaths in patients with CAT occurred during hospice care.

Patient baseline characteristics were determined based on claims during the 180 days preceding the index VTE event and were presented using descrip-

tive statistics. The presence of comorbidities and risk factors was determined using validated coding indices.^{16,20,21} Categorical variables were summarized as proportions. Continuous variables were summarized as mean [SD] or medians and interquartile ranges (IQRs). Cumulative incidence estimates for recurrent VTE, major bleeding, and mortality/hospice care were calculated, along with 95% CIs, assuming competing risks (for recurrent VTE and major bleeding), using the method described by Fine and Gray,²² and graphically depicted as time-to-event curves. An intent-to-treat approach was used and patients were followed until a primary end point, loss to follow-up, or end-of-study period defined as 180 days post-index VTE to match ongoing randomized trials of rivaroxaban in CAT.¹⁰ Cumulative incidence estimates per cancer types constituting at least 10% of the study population were also calculated. Database management and statistical analysis was performed using SAS 9.4 (SAS Institute Inc.) and R version 3.1.2 (The R Foundation for Statistical Computing) with the accompanying cmprsk package.²³

Results

A total of 949 patients with active cancer and a primary diagnosis of VTE were initiated on outpatient anticoagulation therapy with rivaroxaban within 30 days of the index event and included in this analysis. Baseline demographics, comorbidities, and medication use are reported in Tables 1–3. The median time from index VTE to first outpatient rivaroxaban fill was 2 days (IQR, 1, 5), and median time between first and last rivaroxaban prescription was 114 days (IQR, 47, 180). The mean age of identified patients was 62.5 [12.8] years, 45.6% were men, and pulmonary embolism (±DVT) was present in 43.6%. Time from the diagnosis of active cancer to index CAT was ≤90 days in 27% of patients, 91 to 180 days for 19%, and ≥181 days for 54%. Cancer sites (not limited to one per patient) for this rivaroxaban-treated cohort were as follows: 25.5% breast, 21.0% genitourinary (including prostate), 17.3% gastrointestinal, 13.2% hematologic, 11.5% lung, 7.4% gynecologic, 5.8% pancreas, and 39.5% other. Metastatic disease was present in 42.6% of patients.

During the 6-month follow-up period, there were 37 cases of recurrent VTE, 22 cases of major bleeding (17 gastrointestinal, 3 intracranial, 1 geni-

Table 1. Baseline Demographics

Variable	Total Cohort, n (%) N=949
Mean age [SD], y	62.5 (12.8)
>65 y	361 (38.0)
Male sex	433 (45.6)
Year of inclusion	
2012	14 (1.5)
2013	294 (31.0)
2014	482 (50.8)
2015	159 (16.8)
Insurance plan type	
HMO	88 (9.3)
POS	50 (5.3)
PPO	528 (55.6)
Other	280 (29.5)
VTE type	
DVT only	535 (56.4)
PE (±DVT)	414 (43.6)
Time from index event to first anticoagulant claim, d (median, IQR)	2 (1, 5)
Time between first and last rivaroxaban prescription, d (median, IQR)	114 (47, 180)
Mean [SD] number of hospitalizations during previous 180 days	0.6 (1.0)

Abbreviations: DVT, deep vein thrombosis; HMO, health maintenance organization; IQR, interquartile range; PE, pulmonary embolism; POS, point of service; PPO, preferred provider organization; VTE, venous thromboembolism.

tourinary, and 1 other bleed), and 105 deaths or hospice claims (0.42 of which occurred during a hospital stay). The 180-day cumulative incidence estimate was 4.0% (95% CI, 2.8%–5.4%) for recurrent VTE, 2.7% (95% CI, 1.7%–4.0%) for major bleeding, and 11.3% (95% CI, 9.2%–13.6%) for mortality/hospice care (Table 4). The cumulative incidence time-to-event curves assuming competing risk for each end point are depicted in Figure 1. Cumulative incidence estimates for recurrent VTE, major bleeding, and mortality/hospice care for each cancer type present in ≥10% of our study population are reported in Table 4.

Discussion

Current recommended first-line treatment for the management of CAT is a LMWH.^{9,11,24,25} This rec-

Table 2. Baseline Comorbidities and Risk Factors	
Variable	Total Cohort, n (%) N=949
Mean [SD] number of Elixhauser comorbidities	14.29 (9.95)
1	73 (7.7)
2	123 (13.0)
3	121 (12.8)
≥4	632 (66.6)
Cancer type	
Breast	242 (25.5)
Genitourinary (including prostate)	199 (21.0)
Gastrointestinal	164 (17.3)
Colorectal	125 (13.2)
Stomach/Esophagus	39 (4.1)
Hematologic	125 (13.2)
Lung	109 (11.5)
Gynecologic	70 (7.4)
Pancreas	55 (5.8)
Other	375 (39.5)
Metastatic disease	404 (42.6)
Inferior vena cava filter	19 (2.0)
Central venous catheter	47 (5.0)
Chronic kidney disease	
Stage 1–2	28 (3.0)
Stage 3	56 (5.9)
Stage 4–5	18 (1.9)
Unstaged	49 (5.2)
Renal dialysis	2 (0.2)
Coagulopathy	93 (9.8)
Obesity	182 (19.2)
Weight loss	106 (11.2)
Paralysis	27 (2.8)
Tobacco use	186 (19.6)
Varicose veins	17 (1.8)
Hip or pelvis fracture	29 (3.1)
Chronic lung disease	245 (25.8)
Pneumonia	151 (15.9)
Hypertension	591 (62.3)
Diabetes mellitus	243 (25.6)
Hyperlipidemia	377 (39.7)
Rheumatoid arthritis/collagen vascular disease	45 (4.7)
Heart failure	93 (9.8)
Depression	122 (12.9)
Psychosis	47 (5.0)
Liver dysfunction	42 (4.4)
Hypothyroidism	158 (16.6)
Anemia	282 (29.7)
Alcohol abuse	24 (2.5)
Drug abuse	10 (1.1)
Ischemic stroke	40 (4.2)
Transient ischemic attack	16 (1.7)
Acute coronary syndrome	34 (3.6)
Inflammatory bowel disease	13 (1.4)

Table 3. Baseline Medication Use	
Variable	Total Cohort, n (%) N=949
Estrogens	31 (3.3)
Erythropoietin-stimulating agents	11 (1.2)
Antiplatelets or NSAIDs	235 (24.8)
ACE inhibitors or ARBs	338 (35.6)
β-blockers	246 (25.9)
Calcium channel blockers	171 (18.0)
Diuretics	223 (23.5)
Digoxin	11 (1.2)
Statin	288 (30.3)
Insulin	51 (5.4)
Noninsulin diabetes drugs	147 (15.5)
Antidepressants	265 (27.9)
Antiulcer drugs	310 (32.7)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; NSAIDs, nonsteroidal anti-inflammatory drugs.

ommendation is based on RCT data showing a lower risk of recurrent VTE and similar bleeding risk with LMWH compared with VKA therapy.²⁶ Guidelines from ASCO, British Committee for Standards in Haematology (BCSH), American College of Chest Physicians (ACCP), and the International Initiative on Thrombosis and Cancer (ITAC-CME) suggest that oral anticoagulants can be considered an option for long-term CAT treatment based on patient preference or if LMWHs are contraindicated or unavailable.^{9,11,24,25} However, there is no consensus on the role of non-VKA oral anticoagulants, such as rivaroxaban, for the management of CAT. ASCO guidelines⁹ recommend against their use, citing insufficient evidence, whereas ITAC-CME guidance says they can be considered in patients not receiving systemic anticancer therapy when other alternatives are not preferred or available.²⁵ The 2016 ACCP guidelines do not provide a preference between VKA and non-VKA oral anticoagulants in patients not receiving a LMWH.¹¹ Regardless of these recommendations, rivaroxaban was used in 19% of patients in 2015 according to a retrospective evaluation of US prescription patterns for CAT.¹² Thus, there remains a great need for additional evidence supporting its use in this population.

Our retrospective administrative claims database study reports on outcomes for >900 patients with active cancer experiencing a VTE and treated

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Table 4. Six-Month Cumulative Incidence Estimates

Cancer Type ^a	Recurrent VTE, % (95% CI)	Major Bleeding, % (95% CI)	Mortality/Hospice, % (95% CI)
Full cohort	4.0 (2.8–5.4)	2.7 (1.7–4.0)	11.3 (9.2–13.6)
Breast	5.0 (2.9–8.5)	2.1 (0.9–4.7)	10.3 (7.1–14.8)
Genitourinary (including prostate)	2.5 (1.1–5.8)	1.0 (0.3–3.6)	8.0 (5.0–12.7)
Gastrointestinal	3.7 (1.7–7.8)	6.1 (3.4–10.9)	13.4 (9.0–19.5)
Hematologic	1.6 (0.4–5.7)	0.8 (0.1–4.4)	4.8 (2.2–10.1)
Lung	6.4 (3.2–12.7)	3.7 (1.4–9.1)	24.8 (17.6–33.6)

Abbreviation: VTE, venous thromboembolism.

^aReported cancer types present in at least 10% of the study cohort.

as outpatients with rivaroxaban, making it the largest assessment of rivaroxaban for CAT published to date and allowing for analysis by active cancer subtypes. During the 6-month intent-to-treat follow-up period, we observed overall incidences of recurrent VTE and major bleeding consistent with those reported in prior prospective observational studies of rivaroxaban in CAT.^{19,27} Mantha et al¹⁹ conducted a single-arm prospective cohort study of 200 patients with CAT, showing a 6-month cumulative incidence of recurrent VTE and major bleeding with rivaroxaban of 4.4% (95% CI, 1.4%–7.4%) and 2.2% (95% CI, 0%–4.2%), respectively. These clinical events were identified through a search of patient clinical notes. In a subset of 146 patients with cancer identified from the multicenter, prospective, noninter-

ventional XALIA study, VTE recurrence and major bleeding rates of 3.4% (95% CI, 1.1%–7.8%) and 1.4% (95% CI, 0%–4.9%), respectively, were reported.²⁶ Unlike the study by Mantha and colleagues, end points in XALIA were adjudicated by a masked central committee.

Our results are also in line with rivaroxaban data from RCTs.²⁸ In 354 patients diagnosed with cancer at baseline or during anticoagulation treatment and randomized to receive rivaroxaban (15 mg twice daily for 21 days followed by 20 mg daily) in the pooled EINSTEIN trial population, the incidence of recurrent VTE was 5% and the incidence of major bleeding was 2% over a mean follow-up of 6 months.²⁸ Of note, the patients with CAT who received rivaroxaban did not demonstrate a higher rate of recurrent VTE (hazard ratio [HR], 0.67; 95% CI, 0.35–1.30) and exhibited less major bleeding (HR, 0.42; 95% CI, 0.18–0.99) compared with those treated with enoxaparin and bridged to VKA.

Certain types of cancers are known to be associated with higher incidence of VTE recurrence, including lung and gastrointestinal malignancies^{29,30}; conversely, breast cancer and hematologic malignancies are associated with lower recurrent VTE risks. Therefore, it is important to consider the distribution of cancer types when evaluating VTE event rates in CAT studies. The prevalence of lung and gastrointestinal cancer in the current study was 11.5% and 17.3%, respectively, compared with 11.5% and 12% in the study by Mantha et al,¹⁹ 3.4% and 13.7% in XALIA,²⁷ and 7.4% and 14.3% in the rivaroxaban arm of EINSTEIN.²⁸ The relative similarities in overall prevalence of these higher-risk cancer types support the comparable rates of rivaroxaban-associated recurrent VTE observed.

Figure 1. Cumulative incidence time-to-event curves for recurrent venous thromboembolism, major bleeding, and mortality/hospice care. For this analysis, the time to death/hospice care was assigned as the date of in-hospital death or last date of service associated with the hospice claim.

Incidence of the pooled mortality/hospice end point with rivaroxaban in our study was 11.3%. This varies somewhat from the approximate 6-month mortality rates reported in rivaroxaban-treated patients in the study by Mantha et al¹⁹ (17.6%), the subgroup of patients with cancer in the XALIA study (4.8%),²⁷ and the subgroup of patients with active cancer in EINSTEIN²⁸ (17%). The comparatively large variation in mortality in these different CAT trials may be partly explained by differences in study methodology, but is most likely driven by differences in study population. Approximately 90% of deaths seen in CAT studies are due to cancer progression rather than complications of recurrent VTE.³ Furthermore, data suggest that rivaroxaban is more likely to be used in less-ill patients with CAT. Of the 557 patients in XALIA who had active cancer at baseline, 26.2% were prescribed rivaroxaban, with the rest receiving standard therapy. The incidence of mortality in these patients (not controlled for differences in patient characteristics) was 4.8% in the rivaroxaban group and 24.7% in the LMWH group.²⁷

There are some limitations related to the retrospective claims database nature of our analysis that deserve mention. Misclassification (measurement error) and selection bias (selection of patients to receive a treatment in a nonrandomized fashion) may affect the internal and external validity of our study.³¹ In addition, information on cancer staging and patient functional status are either unavailable or not well-defined in claims data, which prevented us from describing this CAT population in greater detail. For these reasons, and because of the relatively small sample of patients receiving rivaroxaban in

our data set, we opted not to perform a comparative analyses of rivaroxaban versus LMWH or warfarin. Our study relied on claims contained within the Truven MarketScan databases,¹⁴ which include data on commercially insured people (with employer-sponsored health plans) or those with Medicare supplemental plans. Therefore, our study may not be generalizable to the US population as a whole. Moreover, the MarketScan databases do not report on out-of-hospital death. The need for us to use hospice care as a surrogate for out-of-hospital death¹⁸ along with the fact that we followed patients beginning with their first outpatient prescription for rivaroxaban (and not evaluating outcomes during the index VTE encounter) may have resulted in an underestimation of mortality risk in our study.

Conclusions

The cumulative recurrent VTE and major bleeding event rates of 4.0% and 2.7%, respectively, observed in this rivaroxaban-treated cohort were relatively consistent with those observed in previous studies of rivaroxaban. Our cumulative mortality/hospice rate of approximately 11% was lower than mortality rates observed in some previous CAT studies, perhaps as an artifact of our study population or methodology, and therefore should be interpreted with caution. Once completed, the randomized multicenter SELECT-D trial (ISRCTN86712308) will provide additional data regarding the use of rivaroxaban in patients with CAT, including data on its comparative efficacy and safety compared with the LMWH dalteparin.¹⁰

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The Rittenhouse • Philadelphia, Pennsylvania

(Breakfast and registration begin at 8:00 AM)

Celebrating 10 years!

Moderator:
Clifford Goodman, PhD
Senior Vice President
The Lewin Group

Module I: Who Exactly is the Payer? A View across the Oncology Ecosystem

Module II: Meet the NCCN Guidelines® Panel Experts

Module III: Incorporating the Patient Voice in Shared Decision Making

By attending, professionals will be able to:

- Hear directly from NCCN Guidelines® Panel Members;
- Improve working knowledge of key business, policy, coverage, reimbursement, informational, and operational issues in oncology;
- Gather valuable insights into developing effective strategies for navigating the various constituencies in cancer care.

Visit NCCN.org/academy to enroll and to access the complete program curriculum.

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