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Full Length Article

Effectiveness and safety of outpatient rivaroxaban versus warfarin for treatment of venous thromboembolism in patients with a known primary hypercoagulable state

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ABSTRACT

Introduction: Screening for primary hypercoagulable states (PHSs) in venous thromboembolism (VTE) patients was not mandated in the EINSTEIN trials; and therefore, few patients with a known PHS were available for analysis. We sought to assess the effectiveness and safety of rivaroxaban versus warfarin for treatment of VTE in patients with a known PHS.

Methods: Using MarketScan claims data from 1/2012-9/2015, we identified adults with a primary diagnosis of VTE during a hospitalization/emergency department visit (the index event), with ≥180-days of continuous insurance coverage prior to the index event, a documented diagnosis for a PHS and newly-initiated as an outpatient on rivaroxaban or warfarin within 30-days of the index VTE. Rivaroxaban and warfarin users were 1:1 propensity-score matched. Balance between cohorts was evaluated by inspecting standardized differences for baseline covariates (< 0.1 considered well-balanced). Patients were followed up to 12-months from the index event or until occurrence of an endpoint, switch/discontinuation of index oral anticoagulation or insurance disenrollment. Rates of recurrent VTE and major bleeding were compared using Cox regression and reported as hazard ratios (HRs) with 95% confidence intervals (CIs).

Results: We matched 403 rivaroxaban and 403 warfarin patients with VTE and a known PHS. All baseline covariates had a standardized difference < 0.1. Rivaroxaban use was associated with a non-significant reduction in recurrent VTE (HR = 0.70, 95%CI = 0.33–1.49) and major bleeding (HR = 0.55, 95%CI = 0.16–1.86) versus warfarin.

Conclusions: In routine practice, the effectiveness and safety of rivaroxaban versus warfarin in VTE patients with a known PHS appears to be similar to that observed in the EINSTEIN trial program.

1. Introduction

Primary hypercoagulable states (PHS), including factor V Leiden, prothrombin gene mutation and protein C, S and anti-thrombin deficiency, range in their thrombotic potential and prevalence (with estimates ranging from < 0.5 to 5% depending on the specific state and patient ethnicity) [1]. Screening for known PHSs is not routinely performed in clinical trials evaluating anticoagulation strategies for treatment and secondary prevention of venous thromboembolism (VTE). Within the EINSTEIN clinical trial program, which studied the efficacy and safety of rivaroxaban versus enoxaparin/vitamin K antagonist (VKA) in patients experiencing a VTE, only 482 (5.8%) patients had a known PHS at baseline [2–4]. Among patients with a known PHS, the rate of recurrent VTE in the pooled EINSTEIN trial population appeared nominally lower in patients randomized to rivaroxaban (1.2%) versus warfarin (2.1%) (p-value not provided). Moreover, data on bleeding rates among EINSTEIN patients with known PHS have not been reported.

In this real-world study, we sought to assess the effectiveness and safety of outpatient rivaroxaban versus warfarin for treatment and

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secondary prevention of VTE in patients with a known PHS.

2. Methods

This study was written in compliance with the RECORD (REporting of studies Conducted using Observational Routinely-collected health Data) statement [5]. We performed a retrospective claims database analysis of patients using the United States (US) Truven Health Analytics MarketScan claims data from January 2012 through September 2015. MarketScan combines two separate databases, a commercial and a Medicare supplemental database, to cover all age groups, and contains claims from over 100 employers, health plans and government and public organizations representing about 170 million covered American lives [6]. Individuals enrolled in the MarketScan databases are largely representative of the US population in terms of age, sex and type of health insurance coverage. MarketScan captures health plan enrollment records, demographics, International Classification of Diseases, Ninth-Revision, Clinical Modification (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 de-identified and are in compliance with the Health Insurance Portability and Accountability Act of 1996 to preserve participant anonymity and confidentiality. This study was determined to not constitute research involving human subjects according to 45 CFR 46.102(f), and therefore, deemed exempt from institutional review board oversight.

To be included in the current analysis, adult patients (≥18-years of age) had to have a primary discharge diagnosis code for DVT (ICD-9-CM codes of 451.1, 451.2, 453.40, 453.41, 453.42, 453.8 or 453.9) or pulmonary embolism (PE) (ICD-9-CM codes of 415.1×) during a hospitalization or emergency department visit (the index VTE event) (coding has a positive predictive value up to 89.1%) [7]. 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 VTE event date (which serves as the study's baseline period). Patients with a VTE claim or a prescription claim for an anticoagulant during this baseline period were excluded to increase the likelihood that we were assessing incident (new) VTEs [7]. Patients were required to have a diagnosis code signaling a PHS (ICD-9-CM code of 289.81) during baseline period or the index VTE encounter (prior to initiation of the index oral anticoagulant) [8] and have been newly-initiated as an outpatient on rivaroxaban or warfarin within 30-days of the index VTE event. The ICD-9-CM code of 289.81 includes the following hypercoagulable states: activated protein C resistance, antiphospholipid antibody syndrome, antithrombin III deficiency, factor V Leiden mutation, lupus anticoagulant with hypercoagulable state, protein C and S deficiency, prothrombin gene mutation and systemic lupus erythematosus inhibitor with hypercoagulable state. Use of the ICD-9-CM code 289.81 has been shown to be highly specific (sensitivity of 95.9%, 95%CI = 94.0–97.4%) for identifying laboratory-diagnosed PHSs [8]. No calculations to estimate required sample size were performed; rather it was determined a priori that all eligible patients meeting inclusion/exclusion criteria would be included and analyzed.

Propensity-scores were calculated using multivariable logistic regression incorporating patient demographics, comorbidities, known VTE risk factors and concomitant non-oral anticoagulation medications identified during the 180-day baseline period. Each eligible rivaroxaban user was 1:1 propensity-score matched (using greedy nearest-neighbor matching without replacement and a caliper of 1%) to a warfarin user to minimize the presence of baseline difference between cohorts. Residual differences in baseline characteristics between weighted cohorts were assessed by calculating absolute standardized differences; with difference < 0.1 considered well-balanced [9].

The primary effectiveness and safety end points for this study were the incidences of recurrent VTE and major bleeding. Secondary endpoints included the occurrence of intracranial hemorrhage (ICH) and gastrointestinal bleeding GIB). Recurrent VTE was defined as a subsequent hospitalization or emergency department visit with a primary ICD-9-CM code for DVT and/or PE (positive predictive value = 95% [95%CI = 93–97]) [10]. We defined major bleeding as a bleeding-related hospitalization using the validated claims coding by Cunningham and colleagues [11]. Patients were followed for a maximum of 12-months from the index event or until the occurrence of an endpoint, switch or discontinuation of the index oral anticoagulant (at treating clinician's discretion), insurance plan disenrollment or end-of-study follow-up. Patients were considered to have discontinued oral anticoagulation therapy if a gap ≥14-days was detected between the most recent anticoagulant fill date and the date when there were no days of anticoagulant supply anticipated to be remaining.

Baseline patient characteristics were analyzed using descriptive statistics. Cox proportional hazards regression was performed on the matched cohorts and results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Because all baseline characteristics were balanced after propensity-score matching, the regression analysis included only index oral anticoagulant received as an independent variable. We also performed a sensitivity analysis excluding patients with diagnosis codes for cancer or any cardiac arrhythmia) as they may have higher thrombotic risk or have an antithrombotic indication (despite not receiving anticoagulation therapy during the baseline period). All data management and statistical analysis was performed using SAS version 9.4 (SAS Inc., Cary, NC, USA). A p-value < 0.05 was considered statistically significant in all cases.

3. Results

We included 806 patients (403 rivaroxaban matched to 403 warfarin users) experiencing VTE with a known PHS. The baseline characteristics of the patients are depicted in Table 1. The mean age of the population was 50 ± 14 years and about half of the patients were female. PE ± DVT was present in 53% of patients and 12% of patients had a hospital admission within 180-days of their qualifying VTE event. Mean duration of anticoagulation treatment was ~7-months in both treatment groups.

Following Cox proportional hazard regression, rivaroxaban use was found to be associated with a non-significant 30% reduction in the hazard of recurrent VTE and a 45% relative reduction in the hazard of major bleeding when compared with warfarin (Fig. 1). Rivaroxaban users had a non-significant 53% relative reduction in the hazard of GIB versus warfarin. Only two patients experienced an ICH, with both events occurring in the warfarin group.

Upon sensitivity analysis excluding patients with cancer and/or cardiac arrhythmia, estimates of the relative effectiveness (HR for recurrent VTE = 0.76, 95%CI = 0.35–1.66) and safety (HR for major bleeding = 0.33, 95%CI = 0.04–3.22) for rivaroxaban compared to warfarin remained consistent.

4. Discussion

Our retrospective administrative claims database study reports on > 800 VTE patients with a known PHS who were treated as outpatients with either rivaroxaban or warfarin. During follow-up, we observed incidences of recurrent VTE and major bleeding consistent with those reported for all patients in the EINSTEIN trial program [4]. In a pooled analysis of the EINSTEIN-DVT and EINSTEIN-PE studies, the incidence of symptomatic recurrent VTE was similar between rivaroxaban (2.1%) and standard-therapy patients (2.3%) (HR = 0.89, 95%CI = 0.66–1.19) [4]. The incidence of major bleeding in EINSTEIN was 1.0% with rivaroxaban and 1.7% with warfarin. In our claims study limited to PHS patients, VTE risk was markedly similar to those seen in the EINSTEIN (HR = 0.70, 95%CI = 0.33–1.49) and rates of major bleeding was identical. Thus, these real-world findings of rivaroxaban use in PHS patients are consistent with those of the overall EINSTEIN