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Association between anticoagulant treatment duration and risk of venous thromboembolism recurrence and bleeding in clinical practice

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ABSTRACT

Introduction: This retrospective observational study examined whether anticoagulant treatment duration varies by risks of venous thromboembolism (VTE) recurrence and bleeding.
Materials and methods: VTE patients naïve to anticoagulants were identified from the HealthCore Integrated Research Database between 06/01/2007 and 09/30/2011 and categorized into three groups: provoked, cancer-related, and unprovoked VTE. Treatment duration was from initiation to discontinuation of anticoagulation, based on a 60-day gap in prescription fill unless there was an international normalized ratio test every 42 days. Bleeding risk was estimated using RIETE score, and VTE risk categories were based on ACCP guidelines. Kaplan-Meier curves and Cox proportional hazards models were used to evaluate association between VTE recurrence/bleeding and anticoagulation duration.
Results: Of 2002 patients identified (52.3% males, mean age 57 ± 15 years), 21.4% had provoked, 16.4% had cancer-related, and 62.1% had unprovoked VTE. Average anticoagulant treatment duration was 294 ± 261 days. After adjusting for demographics and clinical characteristics, provoked and cancer-related VTE patients were 32% (95% CI = 14–54%, $P < 0.001$) and 35% (95% CI = 7–70%, $P = 0.013$) more likely, respectively, to discontinue anticoagulants than unprovoked VTE patients. No differences were observed between provoked and cancer-related VTE patients. Patients with an intermediate/high bleeding risk were 26% (95% CI = 14–36%, $P < 0.001$) less likely to discontinue treatment than those with a low bleeding risk.
Conclusions: The observed anticoagulation duration for VTE may not be concordant with guidelines, due to the challenge of counterbalancing risks of VTE recurrence and bleeding. Further studies are needed to explore this.

Introduction

Venous thromboembolism (VTE) is a serious condition that has multiple causes but few warning signs. Approximately 600,000 people experience VTE annually in the United States alone [1]. After stopping anticoagulation treatment, the incidence of recurrent VTE can be as high as 23% within an average of 4.16 years after the first episode [2]. To help manage VTE and prevent recurrence, the American College of Chest Physicians (ACCP) publishes treatment guidelines based on patient risk [3]. Patients are categorized into unprovoked or idiopathic (no cancer diagnosis or transient risk factors), provoked (provoked by a transient risk factor [without a cancer diagnosis]), or cancer-related VTE groups. Patients with unprovoked or cancer-related VTE have a higher risk of recurrence than those in the provoked categories [4,2]. For instance, the presence of cancer increased the risk of recurrent venous thromboembolism by 72% [4].

The 8th ACCP guidelines, which were current at the time of this study, recommend 3 months of anticoagulant therapy for patients with both provoked and unprovoked VTE, followed by an evaluation of the risk-benefit ratio for long-term therapy in the latter group. Patients with active cancer are considered to have a higher probability of

Abbreviations: ACCP, American College of Chest Physicians; CI, confidence interval; DCI, Deyo-Charlson Comorbidity Index; DVT, deep vein thrombosis; HMO, health maintenance organization; HR, hazard ratio; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; INR, international normalized ratio; PE, pulmonary embolism; PPO, preferred provider organization; RIETE, Computerized Registry of Patients with Venous Thromboembolism; SD, standard deviation; VTE, venous thromboembolism.

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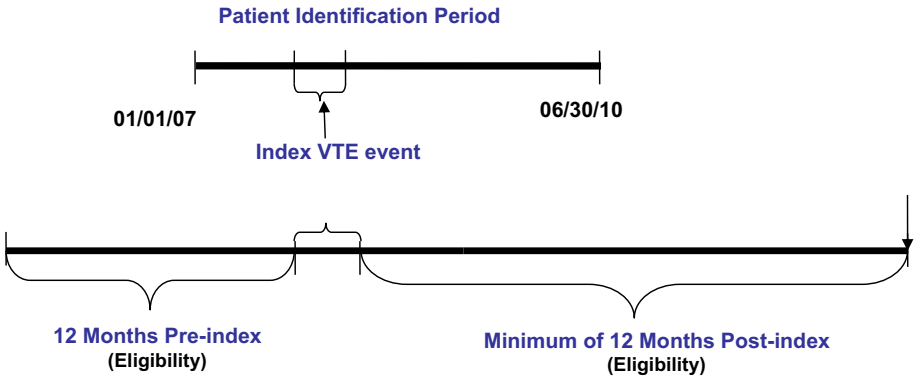

Fig. 1. Study design. VTE, venous thromboembolism.

recurrence. For this reason, a longer duration of anticoagulant therapy is recommended for these patients, compared with patients with provoked risk factors considered reversible [5,6,3,4]. For all categories of patients, any duration of therapy shorter than 3 months is considered suboptimal in the absence of a bleeding event [3]; these recommendations have not changed in the 9th ACCP guidelines [7].

Bleeding complications have been proposed as the main reason for suboptimal treatment duration among patients with VTE [8]. In fact, several studies have suggested that a physician's decision regarding the length of anticoagulant therapy for a particular patient may be primarily influenced by the presence of risk factors for bleeding [8–10]. However, it is important to consider the benefits of anticoagulation (i.e. risk reduction of recurrent VTE) in addition to bleeding risk when determining the optimal duration of anticoagulant therapy [3].

Published guidelines for the treatment of VTE that are accepted and endorsed by professional societies provide a framework for prescribing anticoagulants. However, it is unclear how well these treatment recommendations are followed in real-world practice. This study provides real-world information on the application of anticoagulant treatment guidelines by assessing the duration of anticoagulation therapy in relation to VTE recurrence and bleeding risks.

Materials and Methods

Data

This observational retrospective study used medical and pharmacy claims from the HealthCore Integrated Research Database, which contains data from a large managed care organization that serves 14 geographically dispersed commercial health plans representing approximately 14 million American lives. This database contains diagnostic codes, patient demographics, and pharmacy prescription information. The research was conducted in compliance with state and federal laws, including the Health Insurance Portability and Accountability Act of 1996.

Patient Selection Criteria

Patients aged 18 years or older with the first observed occurrence of VTE diagnosis between June 1, 2007, and September 30, 2011, were included in the study. VTE was identified by the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes for either deep vein thrombosis (DVT) or pulmonary embolism (PE) (451.1x, 451.2x, 451.81, 453.x, and 415.1x). Based on medical claims, the first VTE event was defined as the first inpatient stay or the outpatient visit when the first VTE diagnosis code occurred. The first date of VTE diagnosis was designated as the index date. Patients were excluded if they had no anticoagulation therapy within 7 days after either the inpatient discharge date or the index date of the outpatient visit. Patients also were required to have at least 12 months of continuous health plan eligibility prior to and after the index event. Patients with pharmacy claims for novel oral anticoagulants at any point during the study period also were excluded, because these medications were not approved by the US Food and Drug Administration for the VTE treatment during the study period. Patients with a pre-index history of mechanical valve replacement(s), atrial fibrillation, and/or a prior VTE history also were excluded from the study.

Study Design

This study is a retrospective administrative claims analysis of anticoagulation therapy duration among VTE patients, with regard to their risk for VTE recurrence and bleeding events. Patient risk factors for VTE recurrence and bleeding were evaluated during the baseline period (i.e. 12 months prior to the index date). To examine the relationship between the initial VTE occurrence, bleeding risk factors, and subsequent anticoagulant treatment duration, patients were followed until discontinuation of anticoagulation treatment or change in the

Table 1
Baseline demographics and clinical characteristics of the overall study cohort.

Variables	Total N = 2002
Gender, n (%)	
Male	1,047 (52.3)
Female	955 (47.7)
Age in years, mean (SD)	57 (±15)
Insurance plan type, n (%)	
PPO	1389 (69.4)
HMO	381 (19.0)
Other[a]	232 (11.6)
Geographical region of health plan, n (%)	
Midwest	618 (30.9)
South	543 (27.1)
West	464 (23.2)
Northeast	377 (18.8)
Index VTE setting, n (%)	
Inpatient admission	1,531 (76.5)
Office visit	352 (17.6)
Emergency department visit	119 (5.9)
Length of stay in days, mean (SD)[b]	8.9 (±11.8)
Provoked VTE	8.3 (±11.7)
Cancer-related VTE	10.2 (±13.8)
Unprovoked VTE	8.7 (±11.2)
DCI score, mean (SD)	1.3 (±2.3)
Follow-up period, days, mean (SD)	734 (±245)

DCI, Deyo-Charlson Comorbidity Index, HMO, health maintenance organization; PPO, preferred provider organization; SD, standard deviation; VTE, venous thromboembolism.
[a] Other insurance type includes consumer-directed health plan, point-of-service, and other types.
[b] Among patients (76.5%) identified from index VTE events in hospitalizations.