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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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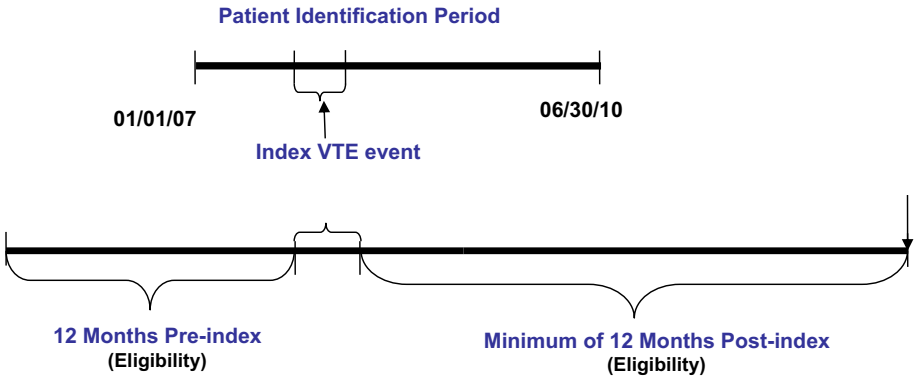

Fig. 1. Study design. VTE, venous thromboembolism.

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.

Table 2
Treatment durations among the overall study cohort (unadjusted).

All anticoagulant treatment	Patients
	N = 2002
Anticoagulant treatment duration in days, mean (SD)	294 (±261)
Categorical anticoagulant treatment duration, n (%)	
Duration ≤90 days	422 (21.1%)
Duration during 91–182 days	446 (22.3%)
Duration during 183–365 days	503 (25.1%)
Duration beyond 365 days	631 (31.5%)
Warfarin treatment	**Patients**
	N = 1868
Warfarin treatment duration in days, mean (SD)	302 (±258)
Categorical warfarin treatment durations, n (%)	
Duration ≤90 days	340 (18.2%)
Duration during 91–182 days	429 (23.0%)
Duration during 183–365 days	502 (26.8%)
Duration beyond 365 days	597 (32.0%)

SD, standard deviation.

risk factor profile (e.g. a VTE or bleeding event, new transient VTE risk factors, such as neurosurgery, orthopedic surgery, trauma, fracture, estrogen therapy, pregnancy/postpartum state, or oral contraceptive use) [3,11], end of health plan enrollment, or end of study (Fig. 1).

Study Measures

VTE recurrence risk groups were defined according to the 8th ACCP treatment guidelines (the most recent guidelines at the time of this study) [3]: patients with cancer-related VTE (with any cancer diagnosis at the inpatient or emergency room visit within one year prior to the index date); patients with provoked VTE by a transient risk factor within three months prior to the index date (without a cancer diagnosis); and patients with unprovoked VTE (with no cancer diagnosis or transient risk factors).

Bleeding risk levels were based on the bleeding risk score methodology of the Computerized Registry of Patients with Venous Thromboembolism (RIETE) [9,10]. RIETE uses six independent predictors to assess risk of bleeding: each predictor is assigned a score of 1, 1.5, or 2 depending on the probability of bleeding, with overall bleeding risk being a sum of these individual risk factor points. The predictors and their respective scores are: recent major bleeding (captured by ICD-9-CM diagnosis codes from claims [12]), 2 points; creatinine levels higher than 1.2 mg/dL (chronic renal dysfunction was used as a surrogate), 1.5 points; anemia, 1.5 points; cancer, 1 point; clinically overt PE, 1 point; and age older than 75 years, 1 point. The overall bleeding risk level for each patient was categorized as high (score higher than 4), intermediate (score of 1–4), and low (score of 0) [9,10].

The study end point was the length of continuous treatment duration, defined as the period from initiation (i.e. the date of the first anticoagulant prescription fill after the index event) through discontinuation of anticoagulant during follow-up. Discontinuation was determined by a combination of prescription fills obtained from pharmacy claims and international normalized ratio (INR) measurements from medical claims (using Current Procedural Terminology code 85610) [13]. Patients were considered to have discontinued treatment if there was a prescription refill gap exceeding 60 days between 2 consecutive anticoagulant prescriptions and there was no intervening claim of INR laboratory tests at least every 42 days [13].

The study end point had two measurements: (1) the length of therapy for all anticoagulant agents (including warfarin, enoxaparin heparin, tinzaparin, dalteparin and fondaparinux) and (2) length of therapy for warfarin only during the follow-up period (minimum of 12 months). In the Kaplan-Meier curves and Cox proportional hazards models, patients were censored at the time of any recurrent VTE or bleeding events if treatment discontinuation was not observed. Covariates used in the multivariable Cox regression models of the two measurements above included age, gender, service setting of the index event, Deyo-Charlson Comorbidity Index score [14], baseline comorbidity conditions including inflammatory bowel disease, neurologic disease associated with extremity paresis, chronic lung disease, hepatic disease, diabetes mellitus, active gastroduodenal ulcer, or malignant hypertension, and any use of antiplatelet agents.

Table 3
Treatment duration by VTE recurrence/bleeding risk levels among the overall study cohort (unadjusted).

Anticoagulant treatment duration by risk groups for VTE Recurrence	Patients	Treatment duration (days)
	N (%)	Mean (SD)
All anticoagulant treatment		
Provoked VTE	429 (21)	258 (±237)
Cancer-related VTE	329 (16)	297 (±271)
Unprovoked VTE	1244 (62)	306 (±265)
Warfarin treatment		
Provoked VTE	400 (21)	264 (±235)
Cancer-related VTE	293 (16)	303 (±268)
Unprovoked VTE	1175 (63)	315 (±262)
Anticoagulant treatment duration by risk levels for bleeding		
Anticoagulant treatment		
Low risk	918 (46)	259 (±248)
Intermediate/high risk	1084 (54)	324 (±267)
Warfarin treatment		
Low risk	842 (45)	269 (±247)
Intermediate/high risk	1026 (55)	330 (±264)

SD, standard deviation; VTE, venous thromboembolism.

Statistical Analysis

Descriptive analyses were conducted, whereby the means and standard deviations (SD) were reported for continuous variables, while frequency and percentage were reported for categorical variables. Kaplan-Meier analysis was used to estimate the proportion of patients who discontinued anticoagulant treatment by VTE recurrence risk and bleeding risk over time.

Two multivariable Cox regression models were performed to examine how treatment duration during the follow-up period varied as a function of all risk groups for VTE recurrence and bleeding risk levels, while controlling for other demographic and clinical factors. One model was performed for any anticoagulant treatment duration and the other for treatment duration with warfarin. The differences in treatment durations by different VTE risk groups or bleeding levels also were presented in adjusted survival curves derived from the two multivariable Cox regression models. All data analyses were conducted in STATA version 11.2 (StataCorp LP, College Station, TX).

To examine the robustness of the study findings, several sensitivity analyses were performed by: (1) including patients with prior VTE medical history, atrial fibrillation diagnosis, or anticoagulation treatment, who were excluded in the primary analysis; (2) using a broader definition of anticoagulant treatment duration with 90 days allowed gap (instead of 60 days as in the main analyses).

Results

Descriptive Results

A total of 2002 patients met the study criteria. Fifty-two percent of the study cohort was male, and the mean age (SD) was 57 (±15) years (Table 1). Most patients (69.4%) were members of a preferred

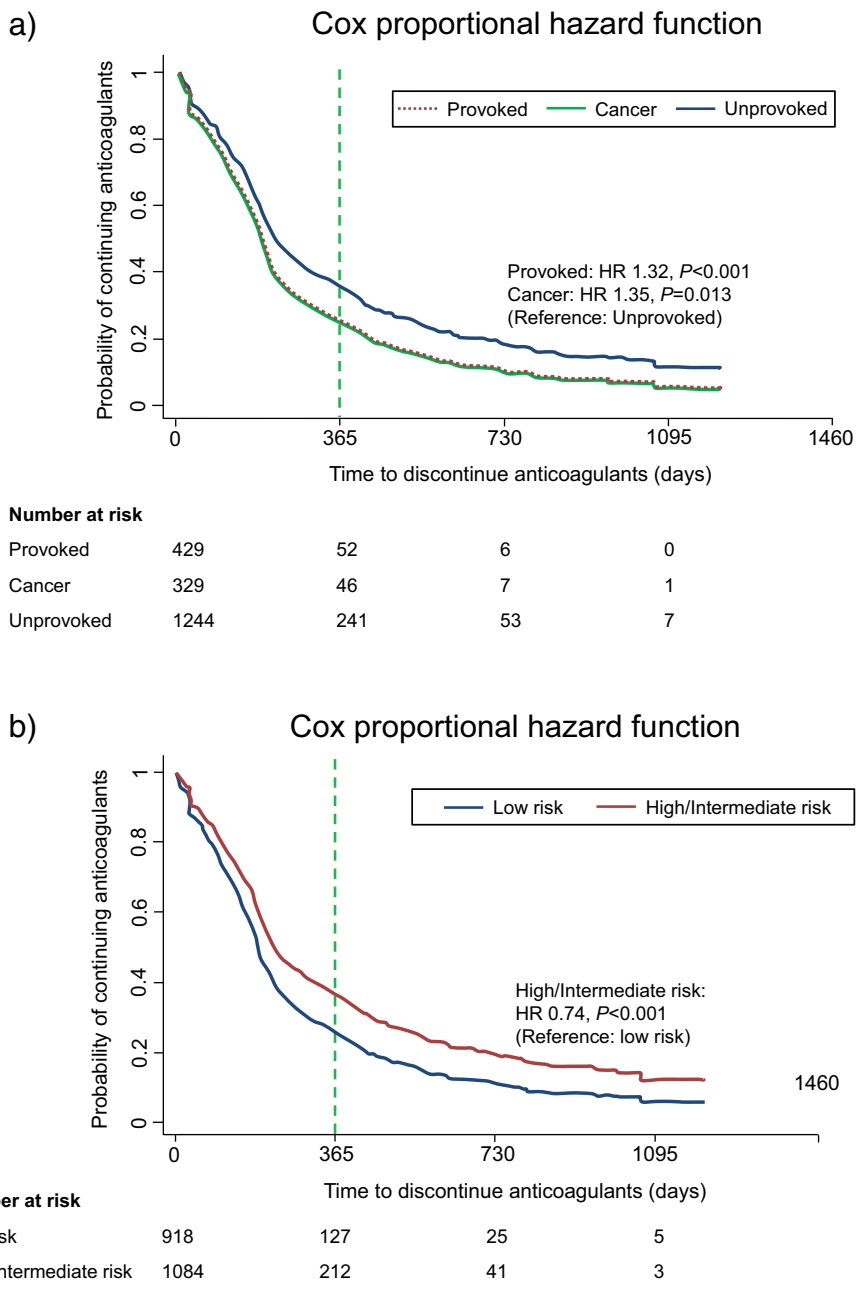

Fig. 2. a Adjusted survival curves by VTE recurrence risk groups (time to anticoagulant discontinuation). HR, hazard ratio; VTE, venous thromboembolism. **b** Adjusted survival curves by bleeding risk levels (time to anticoagulant discontinuation). HR, hazard ratio.

provider organization, with 19.0% belonging to a health maintenance organization and 11.6% having other types of health insurance. The majority (76.5%) of the index VTE events were identified from inpatient hospitalizations (Table 1). Patients with unprovoked VTE accounted for 62.1% of the study cohort, followed by provoked (21.4%) and cancer-related VTE (16.4%). Based on the RIETE bleeding risk score, 45.9% of the study cohort had low, 53.3% had intermediate, and 0.9% had high bleeding risk. Because of the small sample size of the high bleeding risk group, these patients were combined with patients with intermediate risk for the purpose of this analysis.

The mean anticoagulant treatment duration was 294 days (±261). The majority (n = 1868; 93.7%) of patients were treated with warfarin (warfarin alone or warfarin before or after other anticoagulants during the follow-up period). The mean warfarin treatment duration was 302 days (±258); 18.2%, 23.0%, 26.8%, and 32.0% of warfarin users discontinued warfarin within 90 days, 182 days, 365 days, and after 365 days, respectively (Table 2).

With respect to any anticoagulant and warfarin-only treatment, the unprovoked VTE group had the longest treatment duration, followed by cancer-related VTE and provoked VTE (Table 3). Patients at intermediate or high bleeding risk had longer treatment durations for all anticoagulation and warfarin-only treatment compared with patients at low bleeding risk (Table 3).

Multivariable Results

For all anticoagulant treatments, patients with provoked and cancer-related VTE were 1.32 (adjusted hazard ratio [HR] 1.32; 95% confidence interval [CI] 1.14–1.54, $P < 0.001$) and 1.35 (adjusted HR 1.35; 95% CI 1.07–1.70, $P = 0.013$) times more likely to discontinue treatment

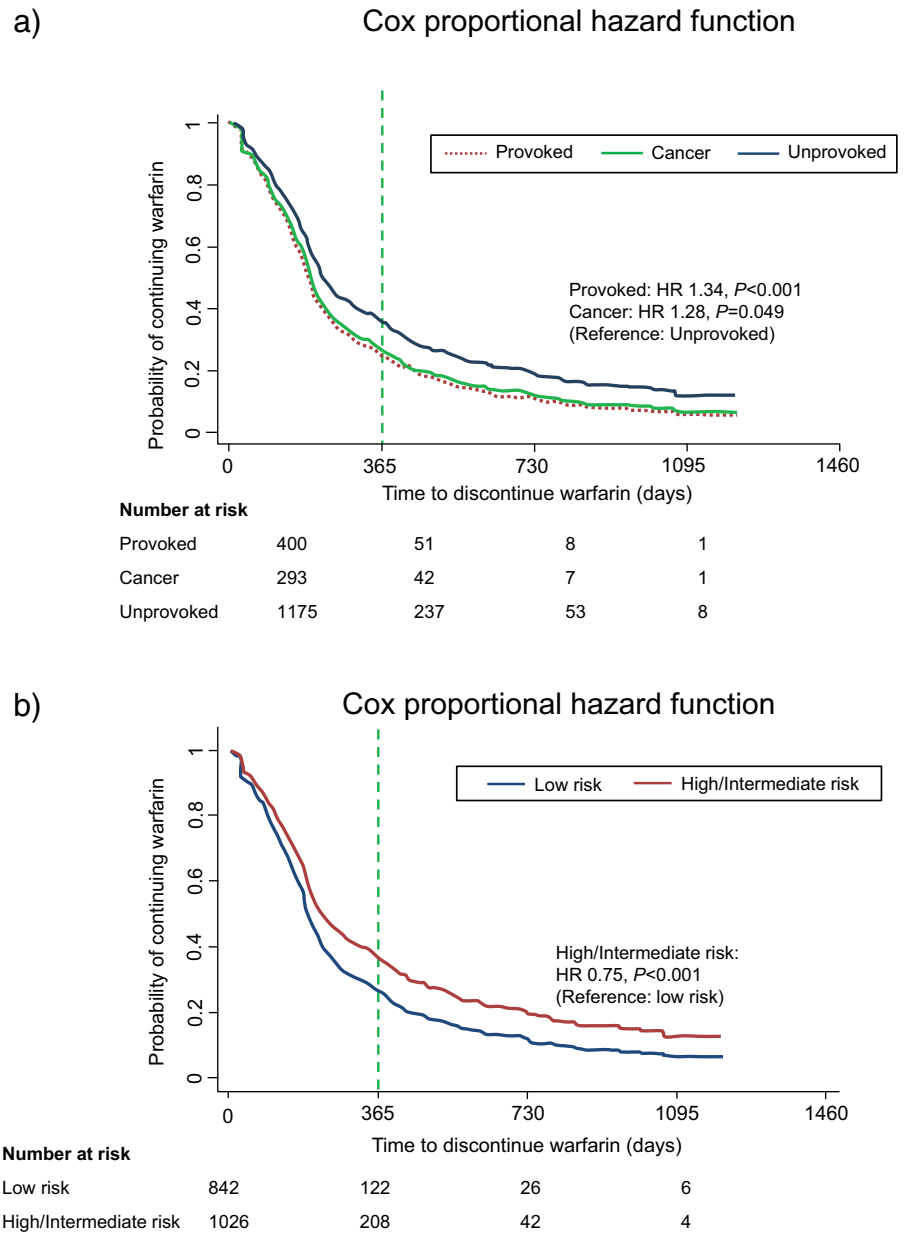

Fig. 3. a Adjusted survival curves by VTE recurrence risk groups (time to warfarin discontinuation). HR, hazard ratio; VTE, venous thromboembolism. **b** Adjusted survival curves by bleeding risk levels (time to warfarin discontinuation). HR, hazard ratio.

during the follow-up period, respectively, compared with patients with unprovoked VTE (Fig. 2a). Patients at high/intermediate bleeding risk were 26% (95% CI 14 — 36%, $P < 0.001$) less likely to discontinue anticoagulant treatment than those at low bleeding risk (Fig. 2b).

Similarly, for warfarin-only treatment, patients with provoked and cancer-related VTE were 1.34 (adjusted HR 1.34; 95% CI 1.14–1.56, $P < 0.001$) and 1.28 (adjusted HR 1.28; 95% CI 1.00–1.64, $P = 0.049$) times more likely to discontinue warfarin, respectively, during follow-up, compared with patients with unprovoked VTE (Fig. 3a). Patients at high/intermediate bleeding risk were 25% (95% CI 12 — 35%, $P < 0.001$) less likely to discontinue warfarin than those at low bleeding risk (Fig. 3b).

Sensitivity Analyses

All results of the sensitivity analyses were consistent with the primary results and did not alter the overall conclusion of this study.

Discussion

This study addressed the association between anticoagulant treatment duration and the VTE and bleeding risk categories in real-world settings. Patients with provoked or cancer-related VTE were found to have significantly shorter anticoagulant treatment durations than patients with unprovoked VTE, while no significant differences were observed between patients with cancer-related and provoked VTE. Patients with VTE who had intermediate or high bleeding risk were found to be less likely to discontinue anticoagulant therapy (either warfarin or any anticoagulant) than those with a low bleeding risk.

Despite the 8th ACCP treatment guidelines recommending 3 months of anticoagulant treatment for patients with provoked VTE and longer-term, indefinite therapy for unprovoked VTE patients, this study found that the average length of therapy for unprovoked VTE patients was only approximately 1.5 months longer than for those with provoked VTE. Similarly, although the 8th ACCP guidelines recommended that patients with cancer-related VTE should be

continuously treated with anticoagulants as long as the cancer is active [3,15], in this study patients with cancer-related VTE did not have a discernibly longer treatment duration than those with provoked VTE. Overall, with respect to the 8th ACCP recommendations, we found that anticoagulant treatment duration by VTE recurrence risk profile is less than optimal in a real-world setting. Based on the 8th and 9th ACCP guidelines, anticoagulant treatment duration should differ according to risk of both VTE recurrence and bleeding and should be assessed on an individual basis [3,7].

Based on our study, patients with VTE who had intermediate/high bleeding risk were less likely to discontinue warfarin or anticoagulant therapy compared with those with low bleeding risk. This seems counterintuitive: all other risk factors being equal, patients with a higher bleeding risk should be treated for shorter durations than patients with a lower bleeding risk. However, the adjusted results in this study showed an opposite trend. Indeed, patients with high bleeding risk may be perceived to have higher VTE recurrence risk; however, these patients were less likely to discontinue anticoagulant therapy even after adjustment for VTE category. A further analysis stratified by provoked, cancer-related, and unprovoked VTE also showed a consistent trend of patients with higher bleeding risk tending to stay on therapy longer (data not shown). Additional studies are needed to investigate whether clinical prediction rules for estimating bleeding risk in patients on oral anticoagulant therapy, such as the modified outpatient bleeding risk index, or RIETE [9] are also predictive of recurrent VTE.

This study found that anticoagulant treatment discontinuation rates within 90 days, which were 18.2% for warfarin treatment only or 21.1% for overall anticoagulant treatments, were higher than those from a previous study, in which a 12.3% treatment discontinuation rate within 90 days was reported in patients hospitalized with VTE [16]. The discrepancy may be due to study measurement differences; in the previous study, discontinuation was defined as lack of a refill within a time period of 2 times last-day-supply, as opposed to the fixed 60-day refill gap used for the current study. Nonetheless, the optimal treatment duration for patients with VTE should be a minimum of 90 days based on the 8th and 9th ACCP guidelines, regardless of whether the VTE event was provoked or unprovoked. Anticoagulant treatment may be discontinued for a variety of reasons, including risk of bleeding, physicians' knowledge of the appropriate treatment durations in the guidelines [17], patients' lack of adherence (possibly associated with their demographic and socioeconomic status [18], or death).

Our study has several limitations. First, it is difficult to predict how long a warfarin prescription will last given the frequent dose changes and number of tablets ingested. We used the algorithm developed by Go and colleagues and validated through electronic medical record/chart review, which has been commonly used to approximate warfarin treatment duration in other observational studies [19,20,13]. Second, we defined provoked VTE as surgical, pregnancy or estrogen related, yet several clinical trials have included estrogen therapy as unprovoked [6]. Third, given the requirement of minimum follow-up time of one year, the study results may not be applicable to those with less than one year of survival (such as cancer patients). Fourth, the database used was for patients who were continually commercially insured, which limits the generalizability to other populations. Fifth, coding errors in administrative data could have contributed to misclassification.

Conclusions

Our study shows that the anticoagulant treatment duration for VTE in clinical practice may not be entirely concordant with guidelines. Although patients with unprovoked VTE had the longest treatment duration, as recommended, those with cancer-related VTE did not have discernibly longer treatment duration than those with provoked VTE. In addition, patients with higher bleeding risk had longer anticoagulant therapy than those with lower bleeding risk, even after adjustments for confounders. This may be due to the challenge of balancing risks of VTE recurrence and bleeding. Future research is needed to explore underlying reasons for anticoagulation treatment duration in patients with first VTE and varying risk profiles in clinical practice.

Role of the Funding Source

Funding for this study was provided by Janssen Scientific Affairs, LLC.

Conflict of Interest

Scott Kaatz is an employee of Hurley Medical Center and receives consulting fees from Janssen Scientific Affairs, LLC. Edith Nutescu is an employee of University of Illinois College of Pharmacy and Hospital and Health Sciences System and receives consulting fees from Janssen Scientific Affairs, LLC. Joyce LaMori, Brahim K. Bookhart, C.V. Damaraju, and Jeff Schein are employees of Janssen Scientific Affairs, LLC. An-Chen Fu, Azza AbuDagga (previous employee), and Hiangkiat Tan are employees of HealthCore, Inc., an independent research organization that received funding from Janssen Scientific Affairs, LLC for the conduct of the study.

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Appendix A Bleeding risk score methodology

Risk factors	ICD-9-CM diagnosis code	Points
Creatinine levels >1.2 mg/dL (chronic renal dysfunction was used as a surrogate)	585.x, 586.x, 403.x	1.5
Anemia	280.00-285.xx	1.5
Cancer	140.xx-208.xx	1
Clinically overt PE	415.1x	1
Age >75 years	NA	1
Recent major bleeding	(see details below)	2
Hemophthalmos, except current injury	360.43	
Retinal hemorrhage	362.81	
Choroidal hemorrhage, unspecified; expulsive choroidal hemorrhage	363.61, 363.62	
Orbital hemorrhage	376.32	
Conjunctival hemorrhage	372.72	
Vitreous hemorrhage	379.23	
Angiodysplasia of stomach and duodenum with hemorrhage	537.83	
Hemoperitoneum	568.81	
Angiodysplasia of intestine with hemorrhage	569.85	
Subarachnoid hemorrhage	430.x	
Intracerebral hemorrhage	431.x	
Other and unspecified intracranial hemorrhage	432.x	
Gastric ulcer with hemorrhage	531.0x, 531.2x, 531.4x, 531.6x	
Gastrojejunal ulcer with hemorrhage	534.0x, 534.2x, 534.4x, 534.6x	
Vomiting of blood	578.x	
Hemorrhage into bladder wall	596.7x	
Hemarthrosis	719.1x	
Hemoptysis	786.3x	
Subarachnoid, subdural, and extradural hemorrhage, following injury	852.x	

ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; N/A, not available; PE, pulmonary embolism.

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