ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

The Association Between Bleeding and the Incidence of Warfarin Discontinuation in Patients with Atrial Fibrillation

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SUMMARY

Aim: While bleeding is a well-known complication of warfarin use and is thought to be a contributory cause of treatment discontinuation, studies quantifying this association are limited. The objective of this study was to quantify the association between bleeding events and subsequent warfarin discontinuation in patients with nonvalvular atrial fibrillation (NVAF). **Methods:** A nested case–control analysis was conducted within a cohort of patients with NVAF newly treated with warfarin. All patients who discontinued warfarin (at least 60 days from last day of warfarin supply) during follow-up were identified as cases and matched with up to 10 controls on age, sex, and duration of follow-up. The index date was defined as the date of warfarin treatment discontinuation of the cases. Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of warfarin treatment discontinuation associated with a bleeding event in the 60 days before the index date. **Results:** The cohort included 24,243 patients who initiated warfarin treatment, of whom 13,482 discontinued treatment during follow-up (cases). Bleeding was associated with an increased risk of warfarin treatment discontinuation (3.55% vs. 0.85%; OR, 4.31; 95% CI, 3.87–4.81). When including only bleeds as the first listed diagnosis, the unadjusted OR was 4.64 (95% CI, 4.10–5.26), and the adjusted OR was 4.65 (95% CI, 4.10–5.27). **Conclusions:** Bleeding was significantly associated with warfarin discontinuation, and thus, the selection of an effective treatment regimen associated with a lower bleeding rate could be a desirable treatment approach.

Introduction

Warfarin, a vitamin K antagonist, is an effective [1,2] and commonly prescribed drug for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). However, there are considerable challenges associated with warfarin treatment [3–6]. Indeed, patients prescribed warfarin need to maintain a narrow therapeutic level of anticoagulation measured by the international normalized ratio (INR). Patients who are underanticoagulated are at increased risk for stroke and those who are overanticoagulated are at increased risk for bleeding [7]. This risk may be reduced with the introduction of the novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban), which have similar or lower rates of thrombotic events compared with warfarin and are associated with a similar or lower risk of bleeding [8–14].

In the real-world setting, warfarin is often underused for stroke prevention in patients with atrial fibrillation (AF) who are eligible for oral anticoagulant treatment [14–17]. One factor that influences the underuse of warfarin is concern about the increased risk for bleeding [18,19]; however, discontinuing or interrupting warfarin treatment for any reason may increase the risk for ischemic stroke [8,20].

It is important to identify and try to prevent events that may lead to warfarin discontinuation in these patients [21,22]. To our knowledge, no observational study has yet evaluated the association between bleeding events and subsequent warfarin discontinuation in patients with AF. Thus, the objective of this study was to quantify the association of bleeding events and subsequent warfarin discontinuation in patients with NVAF.

Methods

Data Source

This study used data from the Optum Research database (Ingenix, Eden Prairie, MN, USA), which includes all paid claims from a large private insurer with more than 35 million members and their dependents across the United States. Members are mostly working individuals under the age of 65 years, but also include those 65 years and older who continue to be insured through

their employer's insurance. The paid claims for both medical and pharmacy benefits are in this database; claims from capitated plans are included as well.

Each claim in the database contains a unique encrypted patient identifier that is used to assemble a longitudinal record of medical and pharmacy services for each member. Eligibility, year of birth, and sex are available for all members in the database (members missing this information were excluded). Individuals in the database are representative of the national commercially insured population for a variety of demographic measures, including age, sex, geographic region, and health plan type. Data available for each medical claim include: dates of service; location of service; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes; physician specialty; and procedure codes in the Physicians' Current Procedural Terminology and the Centers for Medicare and Medicaid provided Common Procedure Coding System. Pharmacy claims include the drug dispensed in National Drug Code format, the date of dispensing, and the quantity and number of therapy-days dispensed.

Patient Population

We first identified a base cohort of all patients (age ≥18 years) with a new diagnosis of AF (ICD-9-CM codes 427.31, 427.32, and 427.3) from 2005 to 2011. A new diagnosis was defined based on the absence of any AF diagnosis in the prior year. We excluded patients with a diagnosis of paroxysmal or valvular AF. We then assembled a study cohort comprising patients who were newly treated with warfarin. Cohort entry was defined by the date of the first warfarin prescription. To be included in the study cohort, patients were required to have at least 1 year of medical history in the database prior to cohort entry, at least 60 days of warfarin treatment, and at least one risk factor for stroke as measured by the $CHADS_2$ score (age ≥75 years, prior stroke or transient ischemic attack [TIA], congestive heart failure [CHF], diabetes, and/or hypertension) in the year prior to cohort entry. Patients with a history of mitral valve prolapse or aortic valve replacement in the year prior to AF diagnosis were excluded.

All patients were followed up from study cohort entry (date of the first warfarin prescription) to the first of the following events: treatment discontinuation (defined by a treatment gap of at least 60 days), death from any cause, end of coverage, or end of the study period (December 31, 2011).

Study Design

A nested case–control analysis was conducted within the study cohort defined above to evaluate the relationship between bleeding and warfarin discontinuation. Cases were patients who discontinued warfarin treatment during follow-up, with the index date set as the date of discontinuation (Figure 1). For each case, up to 10 controls were randomly selected from a case's risk set and matched to the case on age (±10 years), sex, and duration of follow-up (which corresponded to warfarin treatment duration). A sampling with replacement method was used. The controls inherited the index date of their matched cases. In the risk-set sampling, a control could be a case at a later date.

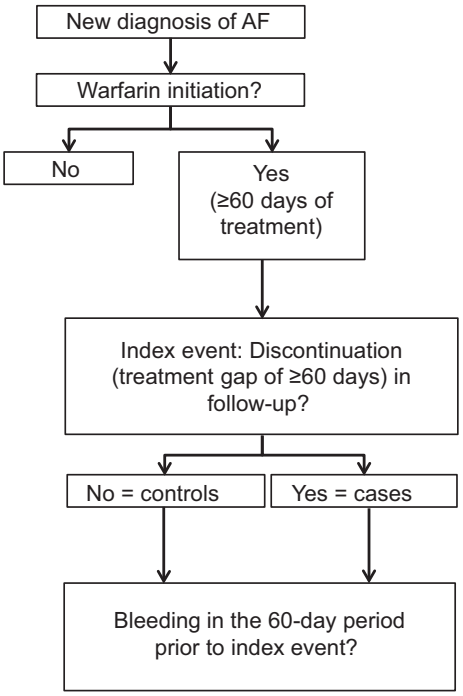

Figure 1 Study design. Cases and controls were matched on age (±10 years), sex, and duration of warfarin treatment. AF, atrial fibrillation.

Bleeding Events

Bleeding events were assessed in a 60-day period prior to index date of discontinuation. These were identified from hospitalized claims confirming in-patient encounters and were defined by specific ICD-9-CM diagnosis codes (Table S1). The ICD-9-CM terms included: gastrointestinal hemorrhage, hemorrhage into bladder wall, hemorrhage of prostate, bleeding female genital tract, hemorrhage during pregnancy, hemarthrosis, epistaxis, hemoptysis, intracranial hemorrhage, intracerebral hemorrhage, hemorrhage of thyroid, retinal hemorrhage, and additional bleeding-related diagnosis codes (Table S1 for complete list). For an individual with multiple bleeding episodes, the bleeding event closest to the index date was selected.

Statistical Analyses

Descriptive statistics were used to summarize the characteristics of the cohort, cases, and matched controls. In the main analysis, we quantified the odds of discontinuing warfarin as a result of a bleeding event. Conditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of warfarin discontinuation associated with bleeding events. All models were adjusted for the following baseline covariates: age, year of cohort entry (i.e., year of warfarin initiation), CHF, hypertension, diabetes, stroke, and TIA, all measured in the year prior to index date. An additional analysis was conducted using $CHADS_2$ score as a covariate instead of the individual variables incorporated into the $CHADS_2$ score.

Sensitivity Analysis

A sensitivity analysis was also conducted in which bleeding events were identified only for patients with bleeding listed as the primary diagnosis.

Results

Patient Population

Of the 351,636 individuals with a new diagnosis of AF identified in the database, 24,243 met the study inclusion criteria (Figure 1). Most cohort members came from older age groups: 1.1% were 18–39 years, 5.1% were 40–49 years, 21.2% were 50–59 years, 33.2% were 60–69 years, and 39.5% were 70 years or older. The majority of patients were male (64.8%). Baseline $CHADS_2$ score was 1 in 34.4%, 2 in 32.0%, and ≥3 in 33.5% of individuals. Within the overall cohort, 88.6% had comorbid hypertension, 33.5% had comorbid diabetes, and 32.8% had comorbid CHF. There was a history of stroke in 19.5% of individuals and a history of TIA in 6.7%. Characteristics of cases and controls at index date are shown in Table 1. Cases were generally similar to the controls.

Among the 24,243 individuals with newly diagnosed AF who met the inclusion criteria, 13,482 had a defined warfarin discontinuation event (index date) within the study period (Figure 2).

The percentage of individuals reporting a bleeding event in the 60 days prior to the index date was higher in cases (individuals with a warfarin discontinuation event) than in controls (individuals without a warfarin discontinuation event). Of the 13,482 cases, 478 individuals (3.55%) had a bleeding event. Among 134,776 controls, 1142 individuals (0.85%) had a bleeding event.

Odds of Discontinuation Associated with Bleeding

When comparing patients with and without bleeding events, the unadjusted OR for warfarin discontinuation was 4.30 (95% CI, 3.86–4.79). The results did not change significantly when the definition of discontinuation was changed from 60 days up to 365 days (data not shown). Based on the conditional logistic regression model, the OR for warfarin discontinuation among individuals with a bleed was 4.31 (95% CI, 3.87–4.81; Table 2). Results for individual $CHADS_2$ components within this model are provided in Table 2. In an analysis using $CHADS_2$ score rather than the components within the $CHADS_2$ score, patients with $CHADS_2$ scores between 2 and 5 had similar odds of warfarin discontinuation compared with those with $CHADS_2$ scores of 1 (OR fell within the range of 0.94–0.98; all 95% CIs included the null value); however, there was a significantly increased risk of warfarin discontinuation in patients with a $CHADS_2$ score of 6 compared with those with a $CHADS_2$ score of 1 (OR, 1.47 [95% CI, 1.23–1.75]).

In the sensitivity analysis, including only bleeds as the first listed diagnosis in hospital claims, there were 369 (2.74%) cases and 811 (0.60%) controls reporting bleeding events. The unadjusted OR was 4.64 (95% CI, 4.10–5.26), and the adjusted OR was 4.65 (95% CI, 4.10–5.27).

Table 1 Characteristics for cases and controls

	Cases		Controls*	
Baseline characteristics	n	%	n	%
Age, years				
18–39	178	1.32	887	0.66
40–49	731	5.42	5243	3.89
50–59	2949	21.87	28,274	20.98
60–69	4238	31.43	47,135	34.97
70–79	2987	22.16	32,286	23.96
80+	2399	17.79	20,951	15.55
Sex				
Female	4624	34.3	46,219	34.29
Male	8858	65.7	88,557	65.71
Year of warfarin initiation				
2006	2557	18.97	29,664	22.01
2007	2321	17.22	25,188	18.69
2008	3687	27.35	36,230	26.88
2009	2351	17.44	22,544	16.73
2010	2064	15.31	16,558	12.29
2011	502	3.72	4592	3.41
$CHADS_2$ score				
1	4826	35.8	47,439	35.2
2	4257	31.58	44,131	32.74
3	2454	18.2	24,862	18.45
4	1198	8.89	11,834	8.78
5	590	4.38	5557	4.12
6	157	1.16	953	0.71
CHF				
Yes	4364	32.37	41,123	30.51
No	9118	67.63	93,653	69.49
Hypertension				
Yes	11,945	88.6	118,874	88.2
No	1537	11.4	15,902	11.8
Diabetes				
Yes	4419	32.78	44,763	33.21
No	9063	67.22	90,013	66.79
Stroke				
Yes	2495	18.51	26,111	19.37
No	10,987	81.49	108,665	80.63
TIA				
Yes	818	6.07	9394	6.97
No	12,664	93.93	125,382	93.03

CHF, congestive heart failure; TIA, transient ischemic attack. *For each case, up to 10 controls were randomly selected from a case's risk set and matched to the case on age (±10 years), sex, and duration of follow-up (which corresponded to warfarin treatment duration). A sampling with replacement method was used. In the risk-set sampling, a control could be a case at a later date.

Discussion

Bleeding is often anecdotally reported as a reason for discontinuation of warfarin treatment [18,19]. Despite fears about bleeding risks with warfarin, few observational studies have been conducted to quantify the association between warfarin use and specific bleeding events. An understanding of how bleeding events impact warfarin discontinuation is important, as interruption of

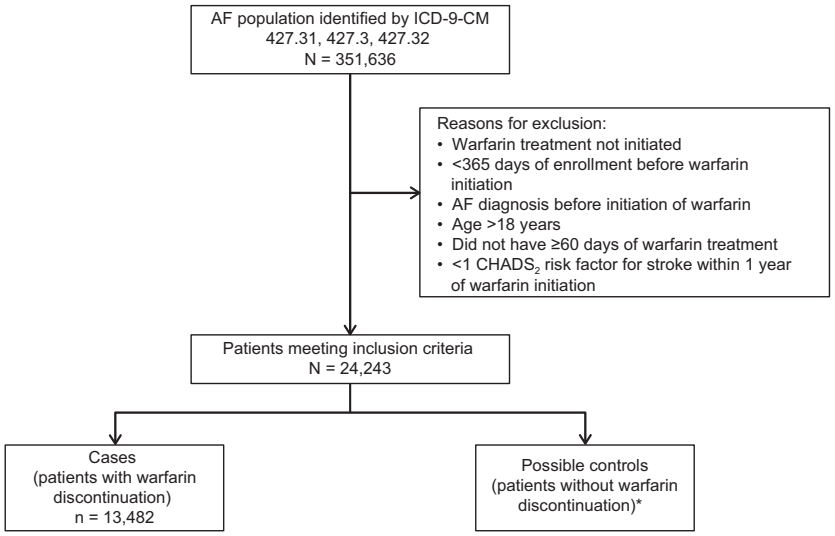

Figure 2 Patient schematic. AF, atrial fibrillation; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code. *For each case, up to 10 controls were randomly selected from a case's risk set and matched to the case on age (±10 years), sex, and duration of follow-up (which corresponded to warfarin treatment duration). A sampling with replacement method was used. In the risk-set sampling, a control could be a case at a later date.

Table 2 Conditional logistic regression model

Parameter	Comparison	Odds ratio	95% Confidence limits	
Bleeding	Unadjusted	4.30	3.86	4.79
	Adjusted	4.31	3.87	4.81
Age, years	18–39 vs. 80+	5.98	4.60	7.78
	40–49 vs. 80+	1.93	1.68	2.23
	50–59 vs. 80+	0.93	0.84	1.03
	60–69 vs. 80+	0.71	0.65	0.78
	70–79 vs. 80+	0.76	0.71	0.81
Year of warfarin initiation	2007 vs. 2006	1.09	1.02	1.15
	2008 vs. 2006	1.21	1.15	1.28
	2009 vs. 2006	1.24	1.17	1.32
	2010 vs. 2006	1.50	1.41	1.60
	2011 vs. 2006	1.34	1.20	1.48
CHF	Yes vs. no	1.06	1.02	1.11
Hypertension	Yes vs. no	1.05	0.99	1.11
Diabetes	Yes vs. no	0.98	0.94	1.02
Stroke	Yes vs. no	0.97	0.92	1.02
TIA	Yes vs. no	0.89	0.81	0.97
$CHADS_2$ score	2 vs. 1	0.94	0.90	0.98
	3 vs. 1	0.94	0.89	0.99
	4 vs. 1	0.96	0.89	1.03
	5 vs. 1	0.98	0.89	1.08
	6 vs. 1	1.47	1.23	1.75

CHF, congestive heart failure; TIA, transient ischemic attack.

warfarin treatment is associated with an increased risk of thrombotic events in patients with AF compared with those without an interruption of treatment [8,20]. In this study, there was a higher proportion of individuals with AF who were diagnosed with a bleeding event in the 60 days prior to discontinuing warfarin compared with those who did not discontinue warfarin treatment.

Several studies have evaluated the risk of bleeding associated with antithrombotic agents, specifically warfarin [21,23,24]. Other studies have evaluated bleeding in the elderly [25–27]. Few studies have evaluated rates of discontinuation in a population with AF treated with an anticoagulant [24,28,29]. This study evaluated the association between bleeding and discontinuation of warfarin in a large population of individuals with a diagnosis of AF (351,636), of whom 24,243 met the inclusion criteria, which included having a history of at least 60 days of warfarin treatment and at least one $CHADS_2$ risk factor for stroke.

One of the limitations of this study was inadequate information in the claims data. This led to some important data not being included in the analysis, including INR values. Additionally, the warfarin discontinuation date (index date) was an approximation calculated by available prescription information. Therefore, the true discontinuation date was unknown and could have been earlier or immediately after the bleeding event. The HAS-BLED score is an important measure of bleeding risk; however, as data for INR and abnormal renal or liver function were not available in the claims data, it was not possible to examine warfarin discontinuation by HAS-BLED score.

An additional limitation may be the underestimation of bleeding events; only bleeding events associated with a hospitalization claim, which the authors assume to be the more serious bleeding events, were identified.

The data from this cohort are generalizable to a US population; however, the elderly population may be under-represented in this cohort. Additional investigation may be needed in patients with AF who are at an advanced age (≥80 years) because they are often considered to be at a higher risk for bleeding, whether or not they are treated with warfarin [28,30]. The results shown here contribute to the growing body of evidence evaluating the association

between warfarin discontinuation and bleeding events in patients with AF. While these analyses do not fully capture all bleeding events during hospitalization, they do suggest that bleeding is significantly associated with warfarin discontinuation.

In conclusion, the association between bleeding events and warfarin discontinuation among patients with AF supports the importance of treatments with a low risk of bleeding.

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Conflict of Interest

TAS, XP, HK, and H-YH are employees of Bristol-Myers Squibb. LA has no conflict of interest to declare; however, he did receive funding to perform the analyses reported here for their cohort.

Author Contributions

All authors had access to the data and were responsible for the concept and design of the study, data analysis/interpretation, and critical revision and approval of the article. In addition, HK was responsible for data collection. HK, XP, and TAS were responsible for drafting the article, and HK and XP were responsible for statistical analyses.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. ICD-9 code definitions.