

Discontinuation/Interruption of Warfarin Therapy in Patients with Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND: Use of warfarin is standard of care for stroke prevention in patients with atrial fibrillation (AF). However, AF patients experience high rates of warfarin discontinuation/interruption, resulting in increased health risks and health care costs. As such, it is important to study the rates and predictors of warfarin discontinuation/interruption in this population.

OBJECTIVES: To determine (a) rates of warfarin discontinuation and interruption and (b) demographic, clinical, and health care-related factors associated with discontinuation and interruption in patients with nonvalvular AF (NVAF) in the usual clinical practice settings in the United States.

METHODS: This retrospective cohort study used the MarketScan Database and included patients (aged ≥ 18 years) with NVAF who were initiated on warfarin. The study period was January 1, 2008, to June 30, 2012. To be included, patients were required to have at least 2 claims with AF diagnosis separated by ≥ 30 days and ≤ 12 months and at least 1 outpatient claim. Warfarin initiation had to occur within 30 days of the AF diagnosis. Patients also had to have continuous enrollment in prescription drug plans from 6 months prior to warfarin use to at least 12 months after warfarin initiation. Patients were followed for 1 year after warfarin initiation. Persistence was defined as warfarin therapy without a gap ≥ 45 days between the end date of the former prescription and the start date of the current prescription or with international normalized ratio (INR) monitoring at least every 42 days. Interruption was defined as a gap in warfarin therapy ≥ 45 days and ≤ 90 days between the end date of the former prescription and the start date of the current prescription and without INR monitoring at least every 42 days. Discontinuation was defined as >90 days without warfarin therapy between the end date of the former prescription and the start date of the current prescription and without INR monitoring at least every 42 days. Chi-square tests were used to analyze categorical variables, and independent samples t-tests were used for continuous variables. Cox proportional hazards regression model was performed to determine factors associated with warfarin discontinuation/interruption, including demographic (e.g., age, gender); clinical (e.g., comorbidities, CHADS₂ score); and health care-related (e.g., hospitalizations or emergency room visits) characteristics. Sensitivity analyses were conducted by varying prescription gaps by 7, 14, and 30 days.

RESULTS: A total of 58,593 patients with NVAF were included. The mean age was approximately 71 years (SD = 12.00) and mean CHADS₂ score was 1.66 (SD = 1.23). The majority of patients were male (60%). During 12 months after warfarin initiation, 45% of patients were persistent with warfarin; 12% had interruption without discontinuation; and 43% had discontinuation. The risk of warfarin interruption or discontinuation was significantly greater in patients who were younger than 65 years (HR = 1.22; 95% CI = 1.19-1.25), lived in the West (HR = 1.07; 95% CI = 1.03-1.11), had

history of anemia (HR = 1.10; 95% CI = 1.06-1.14), had history of bleeding (HR = 1.10; 95% CI = 1.06-1.14), or had history of hospitalization or emergency room visits (HR = 1.11; 95% CI = 1.08-1.13). The significant factors associated with interruption and discontinuation were similar. In the sensitivity analyses, the significant factors associated with discontinuation/interruption were similar across different prescription gaps.

CONCLUSIONS: In the U.S. clinical practice setting, more than 50% of NVAF patients discontinued or interrupted warfarin within 1 year after initiation. Aged < 65 years, history of anemia, and history of hospitalization/emergency room visits were associated with increased risk of discontinuation/interruption. Given the high prevalence of warfarin discontinuation/interruption, health care providers should take a more active role in understanding and addressing the reasons behind patient discontinuation/interruption.

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What is already known about this subject

- Warfarin treatment is associated with significant reductions in the risk of thromboembolic events in patients with atrial fibrillation.
- A high percentage of patients discontinue warfarin within the first year of use. Warfarin discontinuation is associated with stroke risk.
- Factors related to warfarin discontinuation/interruption include bleeding episodes, surgery, inconvenience, return to stable cardiac rhythm, noncompliance, poor anticoagulation control, history of dysrhythmias, lower risk of stroke, history of hospitalization and emergency room visits, and patient age.

What this study adds

- This study used a national database and differentiated between warfarin interruption and discontinuation when studying warfarin utilization patterns.
- More than half of the study participants interrupted or discontinued warfarin therapy during the first year of use: 11.77% interrupted warfarin therapy without warfarin discontinuation, and 43.45% of patients discontinued warfarin therapy with or without warfarin interruption.
- Individuals who were younger than 65 years, had anemia, had bleeding episodes, or were hospitalized or had emergency room visits were at significantly higher risk of warfarin discontinuation/interruption.

Atrial fibrillation (AF) is one of the most commonly encountered cardiac arrhythmias.¹⁻³ Prevalence of AF increases with age, and as a greater subset of the American population ages, the burden of this disease will also increase.⁴ The number of adult individuals with AF in the United States is expected to increase from 5.2 million in 2010 to 12.1 million by 2030.⁵ The steadily increasing population with AF is a concern due to the health risks associated with AF. AF is considered a significant risk factor for thromboembolic events and stroke.⁶ More specifically, patients with nonvalvular AF (NVAF) are 2 to 7 times more likely to experience ischemic stroke than patients without AF.^{1,7}

Administration of anticoagulants such as warfarin is associated with notable reductions in the risk of thromboembolic events in patients with AF, as recommended by practice guidelines such as those by the American College of Cardiology, American Heart Association, and European Society of Cardiology.^{1-4,8-11} Warfarin decreases the risk of stroke by 64% to 86% compared with placebo.¹²⁻¹⁶ Warfarin has also been associated with decreased total health care costs among patients with AF in comparison with patients who were not taking warfarin.¹⁷ However, despite its many benefits, warfarin is associated with adverse events, particularly bleeding and its resulting costs, which likely play a substantive role in warfarin nonpersistence (i.e., discontinuation or interruption).^{10,12,18,19} Other problems with warfarin therapy include the need to frequently monitor the degree of anticoagulation, many drug-drug interactions, drug-food interactions, drug-disease interactions, and genetic polymorphisms affecting warfarin disposition and response.

Generally, studies have found that a high percentage of patients, ranging from approximately 25% to 65%, discontinue warfarin within the first year of use.^{18,20-25} For example, of more than 4,000 AF patients in Fang et al.'s (2010) Anticoagulation and Risk Factors in Atrial Fibrillation Study, approximately 26% discontinued warfarin within 1 year of initiation.²⁰ Patel et al. (2013) found that within 90 days of initiation, 37% of long-term care residents with AF discontinued warfarin; by 1 year postwarfarin initiation, the discontinuation rate increased to 65%.²⁵ A number of factors contribute to warfarin discontinuation among AF patients. A study by Suh et al. (2013) found that recent bleeding increased the probability for warfarin discontinuation by 35%, while Fang et al. found that hospitalization from a hemorrhagic event led to warfarin discontinuation 65% of the time.^{18,20} Other factors related to warfarin discontinuation/interruption include recent bleeding episodes; surgery; frailty/risk of falls (particularly in older patients); return to stable cardiac rhythm; noncompliance; poor anticoagulation control; history of dysrhythmias; lower risk of stroke as indicated by CHADS₂ score (CHADS₂ is a clinical rule that estimates the stroke risk in patients with AF by factoring in congestive heart failure, hypertension, aged ≥ 75 years, diabetes, and prior

stroke/transient ischemic attack [TIA]); history of hospitalization and emergency room visits; and patient age.^{18,20,22-24,26-28}

There are serious clinical consequences to warfarin discontinuation/interruption. As observed by Ewen et al. (2012), patients who experience multiple warfarin interruptions have more than twice the risk for stroke compared with patients with no interruptions.²¹ Studies have also shown significant health care costs related to warfarin discontinuation/interruption.^{27,29} Due to the prevalence of discontinuation/interruption in warfarin-treated AF patients and the associated negative health outcomes and increased health care costs, it is important to study the patterns and predictors of warfarin discontinuation and interruption. Increased understanding of discontinuation and interruption may assist health care professionals and managed care organizations in their attempts to improve warfarin therapy use in AF patients. Because previous studies used small sample sizes, the purpose of the current study was to assess warfarin persistence, discontinuation, and interruption in a broad U.S. patient population. The specific objectives were to determine (a) rates of discontinuation and interruption of warfarin therapy and (b) demographic, clinical, and health care-related factors associated with discontinuation and interruption.

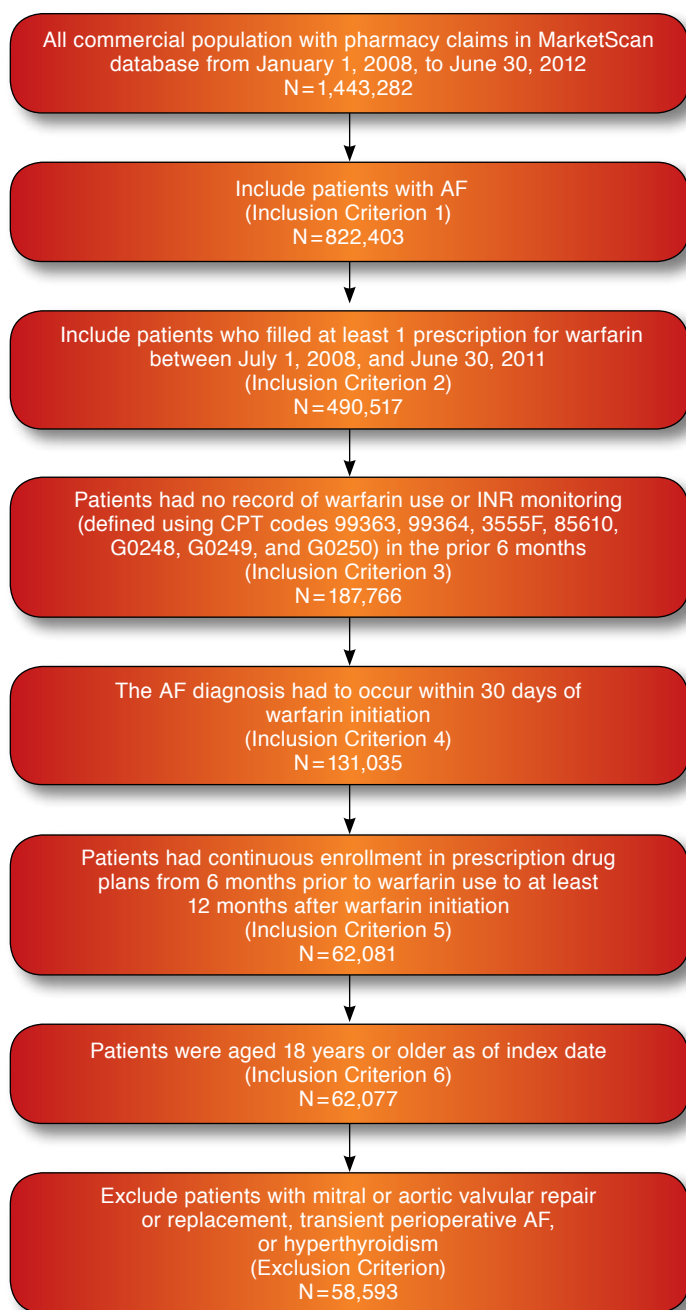
Methods

Study Design

This retrospective cohort study used the Truven MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits databases (January 1, 2008, to June 30, 2012). MarketScan is a de-identified, nationwide medical claims database licensed by Truven Health Analytics. It is compliant with the Health Insurance Portability and Accountability Act and includes enrollment data and insurance claims for inpatient, outpatient, emergency room, pharmacy, and behavioral health care. A unique enrollee identifier is assigned to each individual, which enables cross-linkage of all health care information in the database.

The study population included patients (aged ≥ 18 years) with NVAF who were initiated on warfarin therapy. The inclusion and exclusion criteria for this study are described in Figure 1. To be included, patients with an NVAF diagnosis were required to have at least 2 claims with primary or secondary AF diagnosis, identified by an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code of 427.31, separated by ≥ 30 days and ≤ 12 months and at least 1 outpatient claim with AF diagnosis.²⁹ Warfarin prescription was determined by either generic or brand name (generic name: warfarin sodium and warfarin potassium; brand name: Coumadin, Jantoven, Marevan, Lawarin, Waran, or Athrombin-K and Warfant) from July 1, 2008, to June 30, 2011. Patients had no record of warfarin use or international normalized ratio (INR) monitoring (defined using Current

FIGURE 1 Flowchart of Sample Selection



AF=atrial fibrillation; CPT=Current Procedural Terminology; INR=international normalized ratio.

Procedural Terminology codes 99363, 99364, 3555F, 85610, G0248, G0249, and G0250) in the prior 6 months. This was done to maximize the probability that patients were new warfarin users.^{12,30,31} Warfarin initiation had to occur within 30

days of the AF diagnosis to cover delayed entry of diagnosis codes and maximize the probability that patients were newly diagnosed with AF and were receiving warfarin for stroke prevention.¹² The index date was defined as the day when the first warfarin prescription that met the aforementioned criteria was filled. Patients also had to have continuous enrollment in prescription drug plans from 6 months prior to warfarin use to at least 12 months after warfarin initiation. This was required so that patients could be observed for warfarin persistency patterns for 12 months.²¹ Patients with mitral or aortic valvular repair or replacement (ICD-9-CM codes 394.0, 394.2, 396.0, 396.1, 396.8, v43.3, v42.2, 35.10-35.14, and 35.20-35.28); transient perioperative AF (ICD-9-CM codes 36.10-36.19, 37.10-37.12, 37.31-37.33, 37.40, 35.00-35.04, 35.31-35.39, 35.41-35.42, 35.50-35.56, 35.60-35.63, and 35.70-35.73); or hyperthyroidism (ICD-9-CM codes 242.0-242.9) were excluded to eliminate potential confounding effects in the analysis. Patient enrollment records were used to determine whether patients met the inclusion criteria for age and continuous enrollment.

Measures of Persistence, Interruption, and Discontinuation

Based on the MarketScan database, all medications that patients filled, including warfarin, were obtained from outpatient pharmaceutical claims. The names of medications that patients filled were identified by linking the outpatient pharmaceutical claims to the RED BOOK using the National Drug Code numbers provided as part of MarketScan.³² Patients were followed for 365 days after their warfarin initiation dates for persistence, interruption, and discontinuation status. Persistence was defined as warfarin therapy without a gap ≥ 45 days between the end date of the former prescription and the start date of the current prescription or with INR monitoring at least every 42 days.^{20,21,33} Interruption was defined as a gap in warfarin therapy ≥ 45 days and ≤ 90 days between the end date of the former prescription and the start date of the current prescription and without INR monitoring at least every 42 days.^{20,21,33} Discontinuation was defined as >90 days without warfarin therapy between the end date of the former prescription and the start date of the current prescription and without INR monitoring at least every 42 days.^{18,20} Patients were classified into 4 warfarin persistency categories: (1) persistent, (2) interruption without discontinuation, (3) discontinuation with interruption, and (4) discontinuation without interruption.^{18,21,30}

Independent Variables

The independent demographic, clinical, and health care-related factors included in the study were as follows: age; gender; U.S. census regions (Northeast, North Central, South, West, and Other); and types of health care plans (comprehensive plans, preferred provider organizations [PPO], health maintenance organizations [HMO], and other plans). These variables were determined on the index date. Meanwhile, patient comorbidities

TABLE 1 Baseline Patient Characteristics

Patient Characteristics	All Warfarin Patients		Persistent Patients		Patients with Interruption		Patients with Discontinuation		
	n	%	n	%	n	%	n	%	
Total (n) ^{a,b}	58,593	100.0	26,241	44.8	8,020	13.7	24,332	41.5	
Age (mean ± SD) ^{a,b}	70.89 ± 12.00		72.06 ± 11.27		72.36 ± 11.54		69.13 ± 12.68		
Age ^{a,b}	<65	18,720	32.0	7,363	28.1	2,085	26.0	9,272	38.1
	≥65	39,873	68.0	17,878	71.9	5,935	74.0	15,060	61.9
Gender ^b	Male	34,917	59.6	15,237	58.1	4,628	57.7	15,052	61.9
	Female	23,676	40.4	11,004	41.9	3,392	42.3	9,280	38.1
Region ^{a,b}	Northeast	9,096	15.5	4,107	15.7	1,242	15.5	3,747	15.4
	North central	19,087	32.6	8,828	33.6	2,659	33.2	7,600	31.2
	South	19,037	32.5	8,386	32.0	2,480	30.9	8,171	33.6
	West	11,137	19.0	4,806	18.3	1,618	20.2	4,713	19.4
	Other	236	0.4	114	0.4	21	0.3	101	0.4
Plan type ^{a,b}	Comprehensive	21,177	36.1	9,947	38.8	3,164	40.4	8,066	33.9
	PPO	24,041	41.0	10,452	40.8	3,067	39.1	10,522	44.2
	HMO	7,281	12.4	3,215	12.5	1,068	13.6	2,998	12.6
	Other	4,776	8.2	2,031	7.9	538	6.9	2,207	9.3
CHADS ₂ (mean ± SD) ^{a,b}	1.66 ± 1.23		1.77 ± 1.24		1.73 ± 1.21		1.50 ± 1.21		
CHADS ₂ score ^b	0	10,424	17.8	3,856	14.7	1,185	14.8	5,383	22.1
	1	18,436	31.5	7,964	30.4	2,492	31.1	7,980	32.8
	2	16,909	28.9	8,007	30.5	2,498	31.2	6,404	26.3
	3	8,119	13.9	3,936	15.0	1,178	14.7	3,005	12.4
	4-6	4,705	8.0	2,478	9.4	667	8.3	1,560	6.4
History of congestive heart failure ^{a,b}		14,015	23.9	6,467	24.6	2,066	25.8	5,482	22.5
History of hypertension ^{a,b}		31,722	54.1	14,734	56.2	4,242	52.9	12,746	52.4
History of diabetes mellitus ^b		13,794	23.5	6,525	24.9	1,982	24.7	5,287	21.7
History of stroke or TIA		5,744	9.8	3,127	11.9	812	10.1	1,805	7.4
History of anemia ^b		8,839	15.1	3,730	14.2	1,178	14.7	3,931	16.2
History of bleeding ^b		7,085	12.1	2,948	11.2	925	11.5	3,212	13.2
CCI (mean ± SD) ^b	1.73 ± 1.93		1.79 ± 1.94		1.78 ± 1.91		1.64 ± 1.93		
	0	19,501	33.3	8,109	30.9	2,468	30.8	8,924	36.7
	1	14,261	24.3	6,643	25.3	2,003	25.0	5,615	23.1
	2-3	15,423	26.3	7,032	26.8	2,228	27.8	6,163	25.3
	4-6	7,698	13.1	3,674	14.0	1,089	13.6	2,935	12.1
	>6	1,710	2.9	783	3.0	232	2.9	695	2.9
History of hospitalization or emergency visits ^b		38,586	61.2	15,916	60.7	4,827	60.2	15,113	62.1

^aP < 0.05 for the difference between persistent patients and patients with warfarin interruption.

^bP < 0.05 for the difference between persistent patients and patients with warfarin discontinuation.

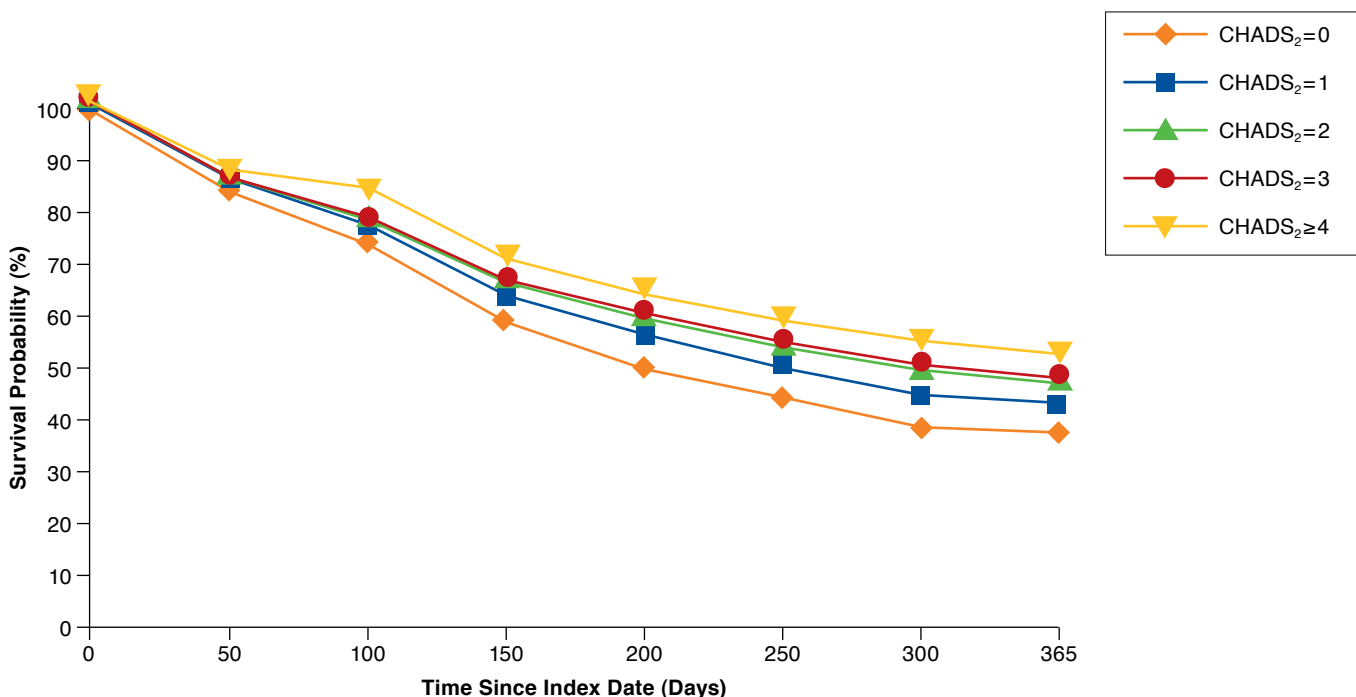
CCI = Charlson Comorbidity Index; HMO = health maintenance organization; PPO = preferred provider organization; SD = standard deviation; TIA = transient ischemic attack.

(congestive heart failure, hypertension, diabetes mellitus, stroke or TIA, and anemia); prior bleeding (gastrointestinal bleeding, intracranial hemorrhage, and other hemorrhage and related procedures based on corresponding ICD-9-CM diagnosis/procedure codes); CHADS₂ score; Charlson Comorbidity Index; and hospitalizations/emergency room visits were also included and determined for the 6-month pre-index period.^{12,18,30,34} The Charlson Comorbidity Index is a measure of health status representing the number of comorbid conditions that a patient has among a total of 22 conditions.³⁵ Patients' medical conditions were obtained from outpatient and inpatient claims.

Statistical Analysis

The rates of discontinuation and interruption in the first year after warfarin initiation were computed. Differences in the distribution of warfarin persistency categories between patients with different demographic (e.g., age and gender); clinical (e.g., comorbidities and CHADS₂ score); and health care-related (e.g., hospitalizations or emergency room visits) characteristics were compared. Chi-square tests were used for categorical variables, and independent samples t-tests were used for continuous variables. To identify demographic, clinical, and health care-related

FIGURE 2 Kaplan-Meier Graph of Time to First Warfarin Discontinuation/Interruption Stratified by CHADS₂ Score



factors associated with warfarin therapy status, patients with warfarin interruption or discontinuation were combined into a discontinued/interrupted group to strengthen study power in the main analysis. The time to first warfarin discontinuation/interruption was depicted using the Kaplan-Meier method, and Kaplan-Meier curves were compared using log-rank test.^{24,30}

A Cox proportional hazards regression model was performed to examine demographic, clinical, and health care-related factors associated with warfarin discontinuation/interruption. The proportionality assumption of the Cox regression model was tested by graphing Kaplan-Meier curves for categorical variables and testing the significance of the interactions between study variables and warfarin persistence time. The Kaplan-Meier curves were reasonably “parallel” across categories of study variables over time. Study findings based on the models including the interaction terms were similar to those without the interaction terms. Therefore, the final findings reported in this study were based on models without the interaction terms for ease of interpretation. Model building in this study was mainly based on relevant literature in addition to a stepwise method with backward elimination (with $P < 0.20$). To differentiate between factors associated with interruption and discontinuation, patients with warfarin interruption and discontinuation were compared separately with persistent

patients. Sensitivity analyses were conducted to assess the robustness of the results by varying the prescription gaps by 7, 14, and 30 days in the analyses.²⁵ All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC), and the statistical significance level was set a priori at 0.05. Institutional review board approval was obtained from the University of Tennessee Health Science Center.

Results

The patient cohort comprised 58,593 patients who met all inclusion and exclusion criteria (Figure 1). The baseline patient characteristics are summarized in Table 1. Mean age was 70.9 years (SD=12.0), mean CHADS₂ score was 1.66 (SD=1.23), and mean Charlson Comorbidity Index was 1.73 (SD=1.93).

Within a 12-month follow-up period, 26,241 (44.79%) patients were persistent with warfarin therapy; 6,895 (11.77%) had interruption without discontinuation; 23,576 (40.24%) had discontinuation without interruption; and 1,881 (3.21%) had discontinuation with interruption. Considering the first episode of interruption or discontinuation only, 26,241 (44.79%) patients were persistent; 8,020 (13.69%) interrupted warfarin; and 24,332 (41.53%) discontinued warfarin. Persistent patients had significantly higher CHADS₂ scores compared with patients who interrupted or discontinued warfarin ($P < 0.05$). A significantly greater number of persistent patients had hyper-

TABLE 2 Demographic, Clinical, and Health Care-Related Factors Associated with Interruption or Discontinuation of Warfarin Based on Multivariate Cox Proportional Hazards Model^a

Variables	Groups	Estimate	P Value	Hazard Ratio	95% CI for Hazard Ratio
Age	≥ 65	-	-	-	-
	< 65	0.20	<0.001	1.22	1.19-1.25
Gender	Male	-	-	-	-
	Female	-0.04	0.001	0.96	0.94-0.98
U.S. census region	Northeast	-	-	-	-
	North central	-0.04	0.035	0.96	0.93-0.99
	South	0.016	0.357	1.02	0.98-1.05
	West	0.06	0.001	1.07	1.03-1.11
	Other region	-0.07	0.425	0.93	0.78-1.11
Health care plan	Comprehensive	-	-	-	-
	PPO	0.01	0.442	1.01	0.98-1.04
	HMO	-0.001	0.940	1.00	0.96-1.04
	Other	-0.02	0.420	0.98	0.94-1.03
Comorbidities	No congestive heart failure	-	-	-	-
	Congestive heart failure	-0.09	<0.001	0.91	0.89-0.94
	No hypertension	-	-	-	-
	Hypertension	-0.09	<0.001	0.92	0.90-0.94
	No diabetes mellitus	-	-	-	-
	Diabetes mellitus	-0.11	<0.001	0.90	0.87-0.92
	No stroke or TIA	-	-	-	-
	Stroke or TIA	-0.33	<0.001	0.72	0.69-0.75
	No anemia	-	-	-	-
	Anemia	0.09	<0.001	1.10	1.06-1.14
	No bleeding	-	-	-	-
Bleeding	0.09	<0.001	1.10	1.06-1.14	
Charlson Comorbidity Index		0.009	0.039	1.01	1.00-1.02
History of hospitalization or ER visits	No	-	-	-	-
	Yes	0.10	<0.001	1.11	1.08-1.13

^aWald chi-square = 858.98; *P* < 0.001.

CI = confidence interval; ER = emergency room; HMO = health maintenance organization; PPO = preferred provider organization; TIA = transient ischemic attack.

tension, congestive heart failure, and diabetes than patients with discontinuation (*P* < 0.05). Significantly fewer persistent patients had anemia and history of bleeding compared with patients who discontinued warfarin (*P* < 0.05). Other significant differences among persistent patients, patients with warfarin interruption, and patients with discontinuation are displayed in Table 1.

Kaplan-Meier estimates indicated that 55.22% of patients either interrupted or discontinued warfarin within the first year of therapy. In stratified analysis, patients who were younger than 65 years were more likely to discontinue/interrupt warfarin than patients who were at least aged 65 years (60.7% vs. 52.7%, respectively; *P* < 0.05). Patients with bleeding were more likely to discontinue/interrupt warfarin than those without bleeding (58.4% vs. 54.8%, respectively; *P* < 0.05). As CHADS₂ scores increased (indicating higher stroke risk), the likelihood of discontinuing/interrupting warfarin decreased (*P* < 0.05; Figure 2).

Predictors of Warfarin Interruption or Discontinuation

In a multivariable analysis based on an adjusted Cox proportional hazards regression model (Wald chi-square = 858.98; *P* < 0.001; Table 2), it was found that individuals who were younger than 65 years (hazard ratio [HR] = 1.22; 95% confidence interval [CI] = 1.19-1.25); lived in the western United States (HR = 1.07; 95% CI = 1.03-1.11); had anemia (HR = 1.10; 95% CI = 1.06-1.14); had bleeding episodes (HR = 1.10; 95% CI = 1.06-1.14); or were hospitalized or had emergency room visits (HR = 1.11; 95% CI = 1.08-1.13) were at significantly higher risk of warfarin discontinuation/interruption. Meanwhile, individuals who were female (HR = 0.96; 95% CI = 0.94-0.98); lived in the north central United States (HR = 0.96; 95% CI = 0.93-0.99); had congestive heart failure (HR = 0.91; 95% CI = 0.89-0.94); had hypertension (HR = 0.92; 95% CI = 0.90-0.94); had diabetes mellitus (HR = 0.90; 95% CI = 0.87-0.92); or had a history of stroke or TIA (HR = 0.72; 95% CI = 0.69-0.75) were at significantly lower risk of discontinuing/interrupting warfarin therapy.

TABLE 3 Analyses of Clinical Factors Associated with Interruption and Discontinuation of Warfarin Therapy and in Sensitivity Analyses Based on Adjusted Cox Proportional Hazards Model

Parameter	Patients with Interruption vs. Persistent Patients		Patients with Discontinuation vs. Persistent Patients		Prescription Gap +7 Days		Prescription Gap +14 Days		Prescription Gap +30 Days	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age ≥ 65	-	-	-	-	-	-	-	-	-	-
Age < 65	0.94	0.89-0.99	1.32	1.28-1.36	1.24	1.20-1.27	1.26	1.23-1.30	1.31	1.28-1.35
Male	-	-	-	-	-	-	-	-	-	-
Female	1.02	0.97-1.06	0.94	0.92-0.97	0.96	0.93-0.98	0.95	0.93-0.97	0.94	0.92-0.97
Northeast	-	-	-	-	-	-	-	-	-	-
North central	0.99	0.93-1.06	0.95	0.92-0.99	0.96	0.93-0.99	0.96	0.93-0.99	0.95	0.92-0.99
South	0.99	0.93-1.07	1.03	0.99-1.07	1.02	0.98-1.05	1.02	0.98-1.05	1.02	0.98-1.05
West	1.09	1.01-1.17	1.07	1.02-1.12	1.07	1.03-1.11	1.06	1.02-1.11	1.05	1.01-1.10
Other region	0.73	0.48-1.13	0.93	0.77-1.14	0.95	0.79-1.41	0.96	0.80-1.15	0.97	0.80-1.17
Comprehensive insurance	-	-	-	-	-	-	-	-	-	-
PPO insurance	0.96	0.91-1.01	1.02	0.99-1.06	1.02	0.99-1.04	1.02	0.94-1.05	1.03	0.99-1.06
HMO insurance	1.07	0.99-1.15	0.98	0.93-1.02	1.00	0.96-1.04	1.00	0.96-1.04	0.99	0.95-1.03
Other insurance	0.89	0.81-0.98	0.99	0.94-1.04	0.99	0.95-1.04	1.00	0.95-1.04	1.01	0.96-1.06
No history of congestive heart failure	-	-	-	-	-	-	-	-	-	-
History of congestive heart failure	1.04	0.98-1.11	0.88	0.85-0.91	0.90	0.88-0.93	0.90	0.87-0.93	0.89	0.86-0.92
No history of hypertension	-	-	-	-	-	-	-	-	-	-
History of hypertension	0.88	0.84-0.93	0.91	0.89-0.94	0.92	0.90-0.94	0.92	0.90-0.94	0.92	0.90-0.94
No history of diabetes mellitus	-	-	-	-	-	-	-	-	-	-
History of diabetes mellitus	0.99	0.93-1.05	0.86	0.83-0.89	0.89	0.86-0.92	0.88	0.86-0.91	0.87	0.84-0.90
No history of stroke or TIA	-	-	-	-	-	-	-	-	-	-
History of stroke or TIA	0.82	0.76-0.90	0.66	0.62-0.69	0.70	0.67-0.73	0.70	0.66-0.73	0.69	0.65-0.72
No history of anemia	-	-	-	-	-	-	-	-	-	-
History of anemia	1.04	0.97-1.11	1.13	1.08-1.17	1.11	1.07-1.14	1.10	1.06-1.14	1.12	1.08-1.16
No history of bleeding	-	-	-	-	-	-	-	-	-	-
History of bleeding	1.03	0.96-1.11	1.13	1.09-1.18	1.11	1.07-1.15	1.12	1.08-1.16	1.12	1.08-1.17
CCI	1.01	0.99-1.03	1.01	1.00-1.02	1.01	1.00-1.02	1.01	1.00-1.02	1.01	1.00-1.02
No history of hospitalization or ER	-	-	-	-	-	-	-	-	-	-
History of hospitalization or ER	0.99	0.94-1.04	1.15	1.11-1.18	1.12	1.09-1.14	1.12	1.09-1.15	1.13	1.10-1.16

CCI=Charlson Comorbidity Index; CI=confidence interval; ER=emergency room; HMO=health maintenance organization; HR=hazard ratio; PPO=preferred provider organization; TIA=transient ischemic attack.

When persistent patients were compared with patients who interrupted warfarin only, fewer factors were significantly associated with interruption than in the main analysis (Table 3). Individuals who lived in the West (HR=1.09; 95% CI=1.01-1.17) were at significantly higher risk of warfarin interruption. Individuals who were younger than aged 65 years (HR=0.94; 95% CI=0.89-0.99); had insurance other than PPO or HMO (HR=0.89; 95% CI=0.81-0.98); had hypertension (HR=0.88; 95% CI=0.84-0.93); or had a history of stroke or TIA (HR=0.82; 95% CI=0.76-0.90) were at significantly lower risk of warfarin interruption. When persistent patients were compared with patients who discontinued warfarin only, the significant factors associated with warfarin discontinuation were consistent with the main analysis. When additional analyses were conducted to determine the factors associated with warfarin discontinuation/interruption by varying prescription gaps (7, 14, and 30 days), the significant factors associated with

discontinuation/interruption were similar to the main analysis when the prescription gaps were increased (Table 3) and decreased (results not shown).

Discussion

In this retrospective observational study involving a large sample of NVAf patients, we examined the rates and predictors of warfarin interruption and discontinuation. More than half of the study participants interrupted or discontinued warfarin therapy during the first year of use: 11.77% of patients interrupted warfarin therapy without discontinuation, and 43.45% of patients discontinued warfarin therapy with or without interruption, a total of 55.22%. Less than half of the study participants, 44.79%, were persistent in their warfarin use. It is noteworthy that this study differentiated between discontinuation and interruption and found that a far greater percentage of patients discontinued warfarin therapy rather than interrupting therapy for a brief period of time.

The combined rates of warfarin discontinuation/interruption estimated in this study are generally consistent with previous studies in the United States. For example, Song et al. (2012) found that 42.6% of AF patients discontinued warfarin (with a gap of at least 90 days between warfarin prescriptions) within the first year of use.²⁴ Deitelzweig et al. (2013) found that 51.4% of NVAF patients discontinued warfarin therapy (with a gap over 60 days between warfarin prescriptions) at least once during follow-up (the mean duration of follow-up was 668 days).³⁶ However, in a study of long-term care patients, Patel et al. found a 1-year discontinuation rate (with a gap over 37 days between warfarin prescriptions) of 65%.²⁵ Likewise, the interruption rate in this study was much lower than the rate suggested by the Raunsø et al. study (2012) using the Danish National Patient Registry.²⁶ In that study, 72% of patients had at least 1 interruption of warfarin therapy (any gap between warfarin prescriptions).²⁶ Variations in study population, study design, and statistical methods may help to explain these differences.

The high combined rate of warfarin discontinuation and interruption among NVAF patients is a cause of concern. Raunsø et al. found that warfarin interruption was associated with increased risk of thromboembolic events and death among AF patients.²⁶ Likewise, Deitelzweig et al. found increased stroke risk during periods of warfarin discontinuation among patients with NVAF.³⁶ This study suggested that history of stroke/TIA served as a protective factor against discontinuation/interruption. Similarly, in the Kaplan-Meier analysis, patients with higher CHADS₂ scores (an indicator of increased stroke risk) had longer time to first incident of warfarin discontinuation/interruption compared with patients who had lower scores. Recall that the calculation of CHADS₂ scores includes history of stroke or TIA. Patients with a history of stroke or TIA may, as a result of these experiences, have greater awareness or knowledge of the health risks associated with AF and the need to adhere to medication regimens to improve health outcomes. Consequently, they may be more likely to remain persistent on warfarin therapy. Physicians also may be less likely to discontinue/interrupt warfarin therapy for patients with a history of stroke or TIA. Given the high prevalence of warfarin discontinuation/interruption and its possible negative outcome on patient health, health care providers should take a more active role in addressing this issue. They should better understand the causes for warfarin discontinuation/interruption, inform patients about the negative consequences of warfarin discontinuation/interruption, and help patients to resolve barriers to warfarin persistence. Health care providers may also consider prescribing alternative anticoagulants, such as newer anticoagulants with more favorable risk-benefit profiles than warfarin and without a need for INR monitoring.³⁷

In the main analysis, the finding of the current study that bleeding and hospitalizations/emergency room visits prior to warfarin initiation are associated with increased risk of warfarin discontinuation/interruption is consistent across prior studies.^{18,20} Bleeding risk may be higher among patients with prior bleeding, which may be a reason for this pattern. Prior

hospitalizations and emergency room visits may be proxy measures for worse health status, and they may serve the same purposes as prior stroke or TIA or the Charlson Comorbidity Index. However, there is a lack of consistency between this study's findings and those of previous studies regarding some other patient factors and their association with warfarin use.^{18,24,25} Consistent with the findings from this study, Song et al. found that older patients had a lower risk of discontinuation,²⁴ and Suh et al. found that being female was associated with reduced likelihood of discontinuation.¹⁸ However, in the same Suh et al. study, older age (greater than 85 years) was associated with increased risk of discontinuation.¹⁸ Patel et al. also found that older age (65 to 74 years) was related to warfarin discontinuation and that being female was associated with warfarin discontinuation.²⁵ Variations in study population, study design, and data analysis methods may again help to explain these differences. Additional research is needed to build a more comprehensive understanding of the relationships among demographic, clinical, and health care-related factors and warfarin persistency patterns, which will help clinicians to determine strategies to improve patient persistence with anticoagulation.

In our subanalyses, when the persistent group was compared with the interruption group only and the discontinuation group only, a few interesting findings emerged. Compared with the main analysis that involved the combined discontinuation/interruption group and noted several factors that increased risk of discontinuation/interruption, the persistent group versus interruption group only analysis found that the only factor that increased risk of interruption was living in the western United States. Moreover, age less than 65 years, a risk factor in the main analysis, seemed to act as a protective factor in the interruption group only analysis. In contrast, factors associated with warfarin discontinuation were consistent with the main analysis. These results suggest that it is useful to distinguish between warfarin interruption and discontinuation in such assessments, since risk and protective factors may vary. In future studies, distinction between interruption and discontinuation and determination of different causes for interruption and discontinuation may reveal more extensive information regarding warfarin persistency patterns and may assist health care providers in developing interventions to improve consistent use of warfarin. Additionally, future research should also further the current literature by determining the clinical and economic implications of warfarin interruption and discontinuation.

Limitations

There are several limitations to this study. First, although we can link some population subgroups to discontinuation/interruption and thus find potential predictors for warfarin discontinuation/interruption, it is impossible to know the reasons for

discontinuation/interruption due to the observational nature of the study. Second, there is a possibility that the method of identifying the discontinuation and interruption periods may underestimate the length of disruptions/interruptions because discontinuations/interruptions were identified when there was an estimated zero tablet remaining in the patients' prescriptions. In reality, patients may interrupt therapy while still possessing medications. Third, this study was based on administrative databases that did not include some clinical parameters related to outcome events, such as body mass index, smoking status, left ventricular ejection fraction, lipid measures, and INR values. Fourth, we did not have inpatient records of medication utilization for patients who were hospitalized during the study period. Therefore, we were unable to determine what medications the patients were given in the hospital. Additionally, we did not consider the possible effects of concomitant medications on warfarin persistence or discontinuation/interruption. Despite these limitations, the findings of the current study made significant contribution to the existing literature by elaborating on the rate of warfarin discontinuation/interruption among NVAF patients and identifying predictors of discontinuation/interruption using a national database when studying warfarin persistency patterns. The method of identifying discontinuation and interruption for this study is generally reliable because study findings are consistent with the previous studies. Additionally, the inclusion of INR monitoring also accounted for anticoagulation monitoring services.

Conclusions

In this administrative database study, rates of warfarin use, as well as factors related to warfarin interruption, discontinuation, and persistence were examined in U.S. patients with NVAF. More than 50% of NVAF patients discontinued or interrupted warfarin use during the 1-year follow-up, and patients who were aged less than 65 years and had a history of anemia, bleeding, or hospitalization/emergency room visits were at higher risk of warfarin discontinuation/interruption. Considering the prevalence of warfarin discontinuation/interruption and the possible consequences for patient health, health care providers should take a more active role in understanding the reasons behind patient discontinuation/interruption, counsel patients on the risks and costs of discontinuation/interruption, and help patients identify and resolve barriers to consistent use of warfarin. Health care providers may also want to consider prescribing alternatives anticoagulants, such as newer anticoagulants with more favorable risk-benefit profiles and without a need to monitor INR.

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DISCLOSURES

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Study concept and design were primarily contributed by Liu, Wang, and Phatak, along with the rest of the authors. Qiao, Mardekian, and Liu were primarily responsible for data collection, assisted by the rest of the authors. Data interpretation was performed primarily by Phatak, Claflin, and Abdulsattar, with assistance from the rest of the authors. The manuscript was written primarily by Spivey, Chakrabarti, and Wang, with assistance from the rest of the authors, and revised by Parker, Kachoo, Wang, and Spivey, with assistance from the rest of the authors.

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