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ORIGINAL RESEARCH

Patterns of warfarin use and subsequent outcomes in atrial fibrillation in primary care practices

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Edward Ewen[1]
Zugui Zhang[1]
Teresa A Simon[2]
Paul Kolm[1]
Xianchen Liu[3,4]
William S Weintraub[1]

[1]Christiana Care Health System, Newark, DE, USA; [2]Bristol-Myers Squibb, Princeton, NJ, USA; [3]Indiana University School of Medicine, Indianapolis, IN, USA; [4]Pfizer, Groton, CT, USA

Background: Warfarin is recommended for stroke prevention in high-risk patients with atrial fibrillation. However, it is often underutilized and inadequately managed in actual clinical practice.

Objectives: To examine the patterns of warfarin use and their relationship with stroke and bleeding in atrial fibrillation patients in community-based primary care practices.

Design: Retrospective longitudinal cohort study.

Participants: A total of 1141 atrial fibrillation patients were selected from 17 primary care practices with a shared electronic medical record and characterized by stroke risk, potential barriers to anticoagulation, and comorbid conditions.

Main measures: Duration and number of warfarin exposures, interruptions in warfarin exposure > 45 days, stroke, and bleeding events.

Results: Among 1141 patients with a mean age of 70 years (standard deviation 13.3) and mean follow-up of 3.4 years (standard deviation 3.0), 764 (67%) were treated with warfarin. Warfarin was discontinued within 1 year in 194 (25.4%), and 349 (45.7%) remained on warfarin at the end of follow-up. Interruptions in warfarin use were common, occurring in 32.6% (249 of 764) of patients. Those with two or more interruptions were younger and at lower baseline stroke risk when compared to those with no interruptions. There were 76 first strokes and 73 first-bleeding events in the follow-up period. When adjusted for baseline stroke risk, time to warfarin start, and total exposure time, two or more interruptions in warfarin use was associated with an increased risk of stroke (relative risk, 2.29; 95% confidence interval: 1.29–4.07). There was no significant association between warfarin interruptions and bleeding events.

Conclusion: Warfarin was underutilized in a substantial portion of eligible atrial fibrillation patients in these community-based practices. In addition, prolonged interruptions in anticoagulation were common in this population, and multiple interruptions were associated with over twice the risk of stroke when compared to those treated continuously.

Keywords: cardiovascular disease, primary care, quality assessment, outcomes

Introduction

Atrial fibrillation is the most common sustained cardiac rhythm disorder and represents a growing health problem in the United States.[1] An estimated 6.1 million persons in the US are currently affected, and this number is projected to reach as high as 12 to 16 million by 2050.[2] In addition, atrial fibrillation is associated with significant morbidity and mortality, including increased risk of stroke,[3] heart failure,[4] and premature death.[5] The annual risk of stroke in patients with nonvalvular atrial fibrillation when not anticoagulated is 3%–5%, and atrial fibrillation is thought responsible for 15% of all thromboembolic strokes.[3]

Correspondence: Edward Ewen
Department of Medicine,
Ammon Education Building, Suite 2E70
4755, Ogletown-Stanton Rd, Newark,
DE 19718, USA
Tel +1 302 428 4672
Fax +1 302 428 2569
Email eewen@christianacare.org

Multiple randomized clinical trials have established the effectiveness of warfarin in reducing the risk of stroke in atrial fibrillation patients by approximately two-thirds,[6–10] and published guidelines for stroke prevention in these patients recommend warfarin therapy for those at moderate to increased risk of stroke.[11] Maximizing the potential benefits while reducing the risk of bleeding on warfarin therapy, however, requires careful titration of dose to maintain anticoagulation intensity within a narrow international normalized ratio (INR) range between 2 and 3.[12–14] Despite this evidence, in actual clinical practice, many patients who qualify for oral anticoagulation do not receive it,[15] and among those who do, only half of their time is spent in therapeutic range,[16–22] and one in four discontinue warfarin within 1 year of starting use.[23] Furthermore, when compared to those treated in anticoagulation clinics, those followed in community practices spend on average 11% less time in therapeutic range.[24]

Few studies have examined patterns of warfarin use in terms of discontinuations and interruptions, and none have yet described the relationship of these patterns to stroke and bleeding outcomes.[16,23] We examined warfarin use and interruptions, the quality of anticoagulation, and their relationship with subsequent stroke and bleeding events in nonvalvular atrial fibrillation patients in community-based primary care practices.

Methods

Study setting and population

We conducted a retrospective longitudinal cohort study of atrial fibrillation patients followed in one of 17 adult primary care practices at any point between January 1, 1998, and June 30, 2010. These specific general internal medicine and family medicine practices were chosen for inclusion in this study based on their use of a common office electronic medical record (EMR) over an extended period of time, and were part of a larger health care system, Christiana Care Health System (CCHS), located in northern Delaware and providing 80% of the acute care services to this region. Approximately one-third were involved in resident training, and none were dedicated anticoagulation clinics.

The initial study cohort included all patients who were 18 years or older at the time of atrial fibrillation diagnosis and had had at least one office visit following the date of diagnosis. The diagnosis of atrial fibrillation was determined by the presence of either atrial fibrillation or atrial flutter recorded by a clinician at the point of care on the office problem list (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 427.30 and 427.31). In addition, clinicians could indicate whether the atrial fibrillation was either chronic or paroxysmal at the time of diagnosis. From this cohort, we excluded patients with no office visits following the date of diagnosis, as well as those with a history of mitral or aortic valve repair or replacement, transient perioperative atrial fibrillation, or hyperthyroidism by diagnosis or treatment at any time prior to diagnosis (Appendix 1). Patients were followed from the date of diagnosis to the date of the patient's death or the study end date.

Data sources

Information on demographics, medication use, and clinical variables, including prior ischemic stroke, gastrointestinal and intracranial hemorrhage, congestive heart failure, hypertension, diabetes, alcohol abuse, cirrhosis, renal disease, cognitive dysfunction, and conditions predisposing to falls were obtained using the EMR problem list. The hospital administrative database was used to further identify episodes of stroke, heart failure, and hemorrhages occurring prior to the diagnosis of atrial fibrillation. A $CHADS_2$ stroke-risk score[25] was calculated for each patient at baseline and for each subsequent day of follow-up for time-dependent analysis. Identification of both office and hospital diagnoses were based on the ICD-9-CM codes assigned at discharge in the hospital or on problem entry in the office. Laboratory values, including hemoglobin, creatinine, and INR, were obtained from both the office EMR and hospital inpatient and outpatient laboratory systems. Specific data definitions for potential barriers to warfarin use and predictors of stroke and hemorrhage are included in Appendices 2 and 3. All medications prescribed in the EMR were entered in a structured (codified) manner at the point of care, including dose and instructions, facilitating identification and classification. In addition, every prescription generated recorded the date, quantity, and number of refills. The research use of these databases was approved by the CCHS institutional review board, and procedures were followed in accordance with institutional guidelines.

Warfarin exposure and anticoagulation intensity

Warfarin exposure was determined through a combination of prescription history and INR measurements. The duration of warfarin exposure was based on the start date of the prescription and the calculated number of days supply, based on the dose, quantity supplied, instructions for use, and number of refills. Because warfarin dose is often adjusted

after a prescription is written, a 30-day grace period and a 15-day elimination or washout period was added to each prescription's calculated duration. As a result, gaps of up to 45 days between calculated days of supply were considered continuous therapy. Gaps greater than 45 days were considered continuous if there were intervening INR values at least every 45 days bridging the prescription gap. Gaps greater than 45 days without intercurrent INR values were considered warfarin interruptions if the patient subsequently restarted warfarin. Patients were then categorized as having none, one, and two or more warfarin interruptions (Figure 1). These gaps were considered discontinuations if warfarin was not restarted prior to the study end.

Once warfarin exposures were determined, we then classified these exposure periods in terms of time in therapeutic range. Simple linear interpolation between consecutive INR

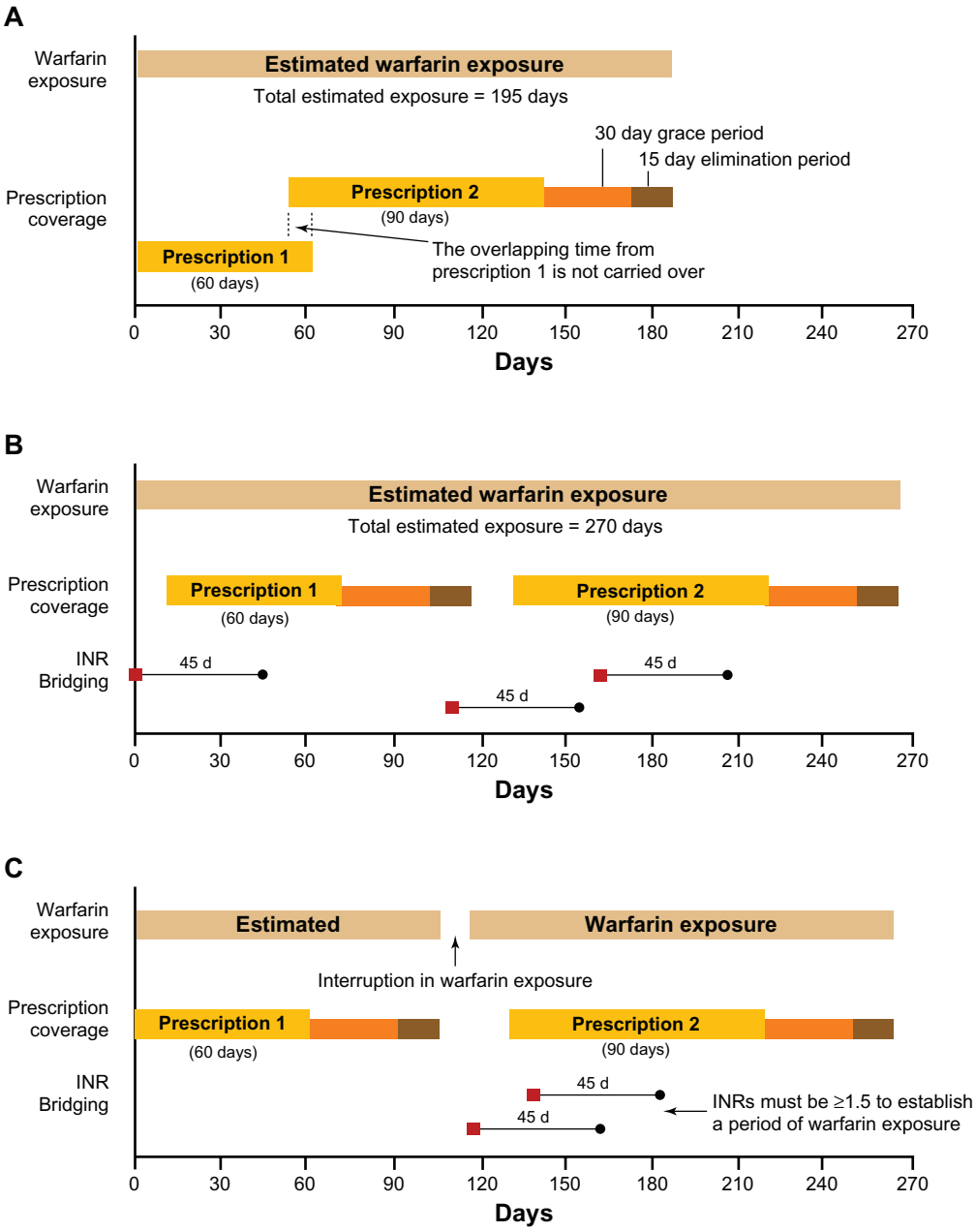

Figure 1 (**A–C**) Calculation of warfarin exposure. Three scenarios demonstrating the methods used to estimate warfarin exposure. (**A**) Calculation of warfarin exposure when consecutive prescription coverage periods overlap. This panel also demonstrates the application of the 30 day grace and 15 day elimination periods. (**B**) Warfarin exposure calculated with INR measurements bridging between periods of prescription coverage. (**C**) Warfarin exposure calculated based on periods of prescription coverage and INR measurements with an interruption in warfarin exposure demonstrated.
Abbreviation: INR, international normalized ratio.

values in a manner similar to that used by Rosendaal et al[26] was used to classify person-time into predefined categories of therapeutic range (INR < 2, subtherapeutic; INR 2–3, therapeutic; INR > 3, supertherapeutic; and INR unknown). If INR values were separated by more than 45 days within a period of warfarin exposure, that time from 45 days after the preceding INR value until the next INR value was classified as unknown. The overall proportion of time in therapeutic range (TTR) was calculated for each patient, excluding the time defined as "unknown." Patients were then categorized as having their proportion of TTR as ≥60% or <60%.

Outcomes

Principal outcomes include the frequency of warfarin interruptions, proportion of time in therapeutic range, stroke or transient ischemic attack (TIA), and hemorrhage. Strokes and TIAs were identified using principal ICD-9 discharge diagnosis extracted from the hospital administrative database. Bleeding events were identified using a combination of primary and secondary hospital discharge diagnosis codes and office EMR problem list entries. All stroke/TIAs and bleeding events were confirmed by manual physician chart review.

Analysis

Descriptive statistics were used to summarize population characteristics overall and in the warfarin treated. Those exposed to warfarin were further categorized into those with none, one, or two or more interruptions in warfarin therapy. The chi-square statistic was used to compare proportions, and the Kruskal–Wallis test was conducted to compare means and medians.

The binary outcomes of warfarin exposure, multiple interruptions in warfarin exposure, and proportion of TTR ≥ 60% were modeled using multivariable logistic regression. Variables associated with each outcome on univariate analysis ($P < 0.15$) were included as potential predictors in each model, and results presented as odds ratios (ORs) with 95% confidence intervals (CI).

The crude incidence rates and 95% CI of first stroke/TIA and bleeding were calculated for each level of warfarin interruption and compared using the Kaplan–Meier method, with differences evaluated using the log-rank test.[27] Because of the time-varying nature of warfarin exposure and potentially long duration of follow-up, nested case-control analyses with matching on time to event were conducted to obtain unbiased estimates of the relative risk of stroke/TIA or bleeding related to multiple interruptions in warfarin exposure.[28–30] A conditional logistic regression model was applied to perform the nested case-control analysis and results expressed as risk ratios (RRs) with 95% CI.

Results

Baseline characteristics and follow-up

Of 121,246 patients followed in these office practices, a total of 1141 patients with atrial fibrillation met the selection criteria (Figure 1). This population accumulated 3848 person-years of time, with a mean of 3.37 years (standard deviation [SD] 2.97, median 2.37, interquartile range [IQR] 1.08–4.93) following their diagnosis of atrial fibrillation. The mean age at diagnosis was 70 years (SD 13 years); more than 68% were aged 65 and older, 48.3% were women, 12.5% were African–American, and 80.7% had a diagnosis of chronic or persistent atrial fibrillation. There was a prior history of stroke or TIA in 11.1%, heart failure in 12.4%, known coronary artery disease in 20.4%, hypertension in 43.1%, and diabetes mellitus in 15.6%. There were 437 (38.3%) patients with a $CHADS_2$ score ≥ 2 and considered at high risk for stroke.

Warfarin exposure

Warfarin was used at some point after diagnosis in 66.7% (n = 764) of the population. Overall, those patients receiving warfarin were older, more often diagnosed with chronic rather than paroxysmal atrial fibrillation, and followed longer than those not receiving warfarin (Table 1). Of those at high risk for stroke ($CHADS_2$ score ≥ 2), 295 (67.5%) received warfarin at some point after diagnosis. There was no significant association between treatment with warfarin and potential barriers to warfarin use considered as a group, even in those at high risk for stroke ($P = 0.36$). When examining predictors of warfarin use (Figure 2), those with chronic atrial fibrillation (adjusted OR, 2.99; 95% CI: 2.19–4.08), age ≥ 75 years (OR, 1.42; 95% CI: 1.07–1.89), African–American (OR, 1.70; 95% CI: 1.10–2.63), or a prior history of heart failure (OR, 1.61; 95% CI: 1.037–2.52) were more likely to receive warfarin. Patients with significant anemia (hemoglobin ≤ 10.0 g/dL, OR, 0.67; 95% CI: 0.48–0.93), hypertension (OR, 0.76; 95% CI: 0.58–0.99), or a diagnosis predisposing to falls (OR, 0.71; 95% CI: 0.51–0.99) were less likely to receive warfarin therapy (c-statistic = 0.66).

During examination of the 764 warfarin-treated patients, there were 1358 patient-years of warfarin exposure during 2857 person years of follow-up time. These patients were followed for a mean of 3.74 years (median 2.78, IQR 1.26–5.57) and were treated with warfarin for a mean of 1.78 years (median 1.09, IQR 0.39–2.38). Warfarin was

Table 1 Baseline characteristics by warfarin use

	Warfarin exposure		
	Exposed (n = 764)	**Not exposed (n = 377)**	***P*-value**
Chronic atrial fibrillation (%)	665 (87)	256 (67.9)	<0.001
Age, mean (SD)	72 (12)	68 (15)	<0.001
Age, years (%)			<0.001
<55	81 (10.6)	91 (24.1)	
55–64	126 (16.5)	65 (17.2)	
65–74	212 (27.7)	77 (20.4)	
≥75	345 (45.2)	144 (38.2)	
Women (%)	361 (47.3)	190 (50.4)	0.32
African–American (%)	106 (13.9)	37 (9.8)	0.05
Risk factors for stroke (%)*			
Stroke or TIA	92 (12)	35 (9.3)	0.16
Heart failure	109 (14.3)	33 (8.8)	0.008
Hypertension	315 (41.2)	177 (46.9)	0.07
Diabetes mellitus	116 (15.2)	62 (16.4)	0.58
Coronary heart disease	166 (21.7)	67 (17.8)	0.12
Peripheral vascular disease	22 (2.9)	8 (2.1)	0.45
$CHADS_2$ stroke risk score*			0.05
0	202 (26.4)	124 (32.9)	
1	267 (34.9)	111 (29.4)	
≥2	295 (38.6)	142 (37.7)	
Potential barriers to warfarin use*			
Gastrointestinal bleeding	48 (6.3)	23 (6.1)	0.91
Alcohol abuse	35 (4.6)	21 (5.6)	0.47
Cirrhosis/hepatitis	54 (7.1)	31 (8.2)	0.49
Cognitive dysfunction	55 (7.2)	32 (8.5)	0.44
Fall risk	129 (16.9)	81 (21.5)	0.06
Anemia†	149 (19.5)	94 (24.9)	0.04
CKD stages 3–5	282 (36.9)	107 (28.4)	0.004
Other antithrombotic therapy (%)			
Aspirin	352 (46.1%)	252 (66.8%)	<0.001
Clopidogrel	77 (10.1%)	31 (8.2%)	0.31
Years followed (SD)	3.74 (3.06)	2.63 (2.63)	<0.001

Notes: *Identified prior to atrial fibrillation diagnosis; †hemoglobin ≤ 10 mg/dL.
Abbreviations: SD, standard deviation; TIA, transient ischemic attack; CKD, chronic kidney disease.

started at the time of diagnosis in 412 patients (53.9%), and over 75% (n = 580) were started within 180 days of atrial fibrillation diagnosis. Within 1 year, 25.4% (194 of 764) had permanently discontinued warfarin use. At the conclusion of the follow-up period, 349 (45.7%) of warfarin-treated patients were still using warfarin. The majority of patients had a single exposure to warfarin (67.4%, n = 515), and once started, 235 (45.6%) of these remained on warfarin for the duration of follow-up.

There were 553 interruptions in warfarin therapy occurring in 32.6% (n = 249) patients, with 129 patients having a single interruption and 120 having two or more interruptions in usage. These interruptions lasted a mean of 339 days (SD 499 days, median 125 days, IQR 31–430 days) and were of decreasing duration as the number of interruptions per patient

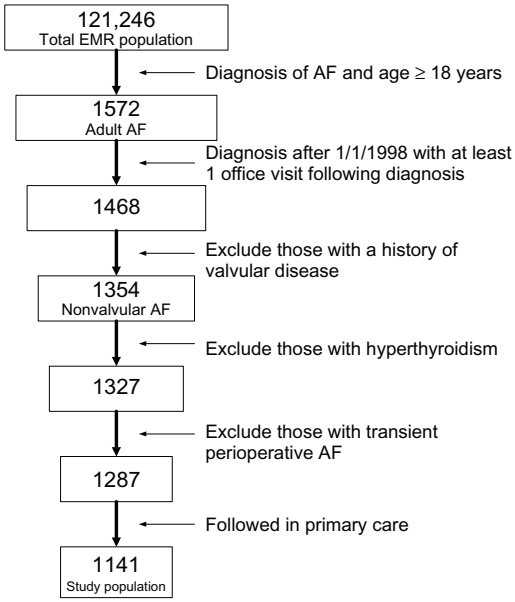

Figure 2 Population and cohort definition.
Abbreviations: EMR, elctronic medical record; AF, atrial fibrillation.

increased ($P < 0.01$). Patients with interruptions in warfarin therapy were younger, followed longer, and were at lower stroke risk than those with no interruptions in therapy, while there was no significant association between the presence of potential barriers to warfarin therapy and the frequency of interruptions (Table 2). In multivariable analysis adjusting for time to warfarin start, total years followed, and demographics (Figure 3), only hypertension significantly predicted freedom from interruption (OR 0.65, 95% CI 0.44–0.96, c-statistic = 0.79) (Figure 4).

Quality of anticoagulation

In patients treated with warfarin, the majority of time spent anticoagulated was classified by our algorithm as unknown (68%, 922 patient-years). When the therapeutic range was known, patients spent 47.3% of their time in therapeutic range (INR 2–3), 40.2% of the time below therapeutic range, and 12.5% above therapeutic range. Only 23.4% of patients spent 60% or more of their time on warfarin in therapeutic range. Age, sex, race, and stroke-risk factors were not predictive of achieving good control, and there were no significant differences in the proportion of time spent in subtherapeutic, therapeutic, and supertherapeutic ranges between those with no, a single, and multiple interruptions in warfarin use.

Stroke and bleeding

In the period following atrial fibrillation diagnosis, there were 107 strokes occurring in 76 patients. The majority of

Table 2 Baseline characteristics by frequency of warfarin interruptions

	Number of warfarin interruptions			*P*-value
	None (n = 515)	1 (n = 129)	≥2 (n = 120)	
Chronic atrial fibrillation	446 (86.6)	108 (83.7)	111 (92.5)	0.10
Age in years, mean (SD)	73 (11)	71 (13)	68 (12)	0.002
Age, years (%)				0.05
<55	45 (8.7)	17 (13.2)	19 (15.8)	
55–64	80 (15.5)	19 (14.7)	27 (22.5)	
65–74	143 (27.8)	37 (28.7)	32 (26.7)	
≥75	247 (48)	56 (43.4)	42 (35)	
Women (%)	239 (46.4)	68 (52.7)	54 (45)	0.38
African–American (%)	63 (12.2)	20 (15.5)	23 (19.2)	0.12
Risk factors for stroke (%)*				
Stroke or TIA	445 (86.4)	119 (92.2)	108 (90)	0.14
Heart failure	77 (15)	15 (11.6)	17 (14.2)	0.63
Hypertension	242 (47)	46 (35.7)	27 (22.5)	<0.001
Diabetes mellitus	93 (18.1)	17 (13.2)	6 (5)	0.001
Coronary heart disease	119 (23.1)	23 (17.8)	24 (20)	0.38
Peripheral vascular disease	14 (2.7)	6 (4.7)	2 (1.7)	0.35
$CHADS_2$ stroke risk score				<0.001
0	111 (21.6)	42 (32.6)	49 (40.8)	
1	178 (34.6)	46 (35.7)	43 (35.8)	
≥2	226 (43.9)	41 (31.8)	28 (23.3)	
Perceived barriers to warfarin Use*				
Gastrintestinal bleeding	31 (6)	11 (8.5)	6 (5)	0.47
Alcohol abuse	21 (4.1)	5 (3.9)	9 (7.5)	0.25
Cirrhosis/hepatitis	37 (7.2)	8 (6.2)	9 (7.5)	0.91
Cognitive dysfunction	34 (6.6)	11 (8.5)	10 (8.3)	0.66
Fall risk	96 (18.6)	18 (14)	15 (12.5)	0.17
Anemia†	108 (21)	23 (17.8)	18 (15)	0.29
CKD stages 3–5	181 (35.1)	49 (38)	52 (43.3)	0.24
Other antithrombotic therapy (%)				
Aspirin	221 (42.9)	69 (53.5)	60 (50)	0.06
Clopidogrel	12 (2.3)	3 (2.3)	1 (0.8)	0.58
Years followed, mean (SD)	2.8 (2.5)	4.6 (3.0)	6.8 (2.9)	<0.001

Notes: *Identified prior to atrial fibrillation diagnosis; †hemoglobin ≤ 10 mg/dL.
Abbreviations: SD, standard deviation; TIA, transient ischemic attack; CKD, chronic kidney disease.

these strokes occurred in the warfarin users (95 strokes in 65 patients). When focusing on first stroke events and comparing unadjusted rates, those patients with multiple interruptions in warfarin therapy had an increased incidence of stroke compared to those with no interruptions in treatment (Table 3). In nested case-control analysis adjusting for sex, race, and $CHADS_2$ stroke risk, those with two or more warfarin interruptions were at significantly higher risk of stroke compared to those with no interruptions (RR 2.29, 95% CI 1.29–4.07, $P = 0.005$).

There were 73 bleeding events (40 major and 33 minor) occurring after atrial fibrillation diagnosis in 64 patients. Of these events, 18 involved intracranial bleeding and 55 were due to gastrointestinal bleeding. The number of warfarin interruptions appeared to have no impact on unadjusted bleeding rates and, after multivariable adjustment using the nested case-control analysis, there were no significant differences found between groups.

Discussion

In this retrospective analysis of 1141 atrial fibrillation patients followed in these community-based primary care practices, we found significant deficiencies with both the initiation and subsequent maintenance of warfarin therapy. Nearly one-third of those at high risk for stroke ($CHADS_2$ stroke-risk score ≥ 2) never received warfarin therapy despite the absence of identified barriers to anticoagulation. When examining patterns of warfarin use, we found that while it was often

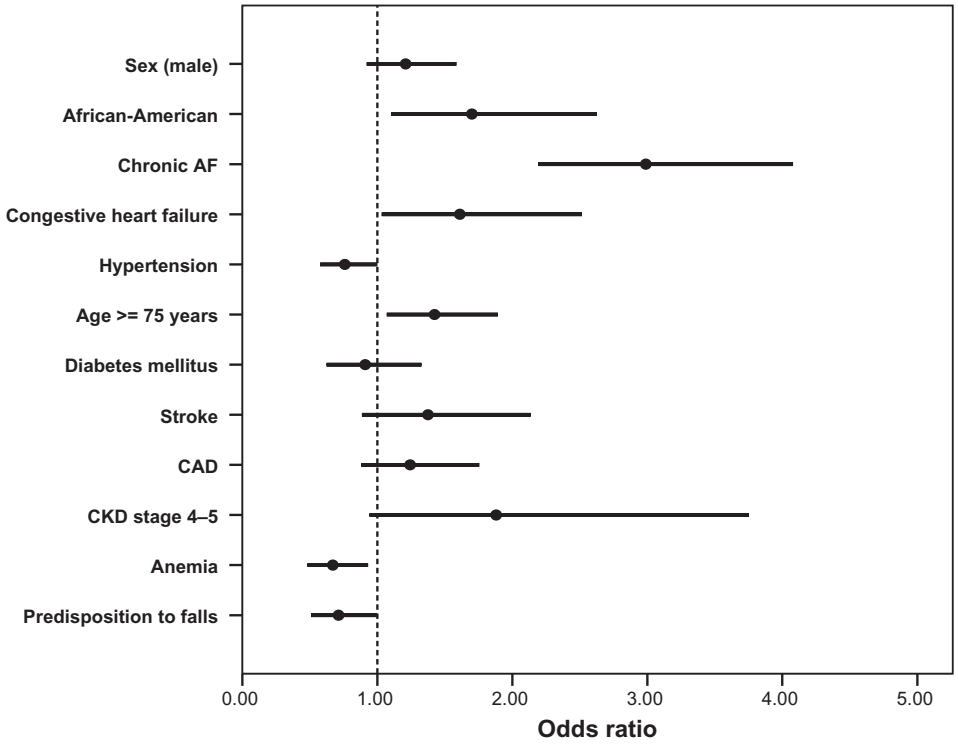

Figure 3 Forest plot of the predictors of warfarin use.
Notes: Odds ratio with 95% confidence interval. Anemia = hemoglobin ≤ 10 mg/dL.
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease (MDRD stages 4–5).

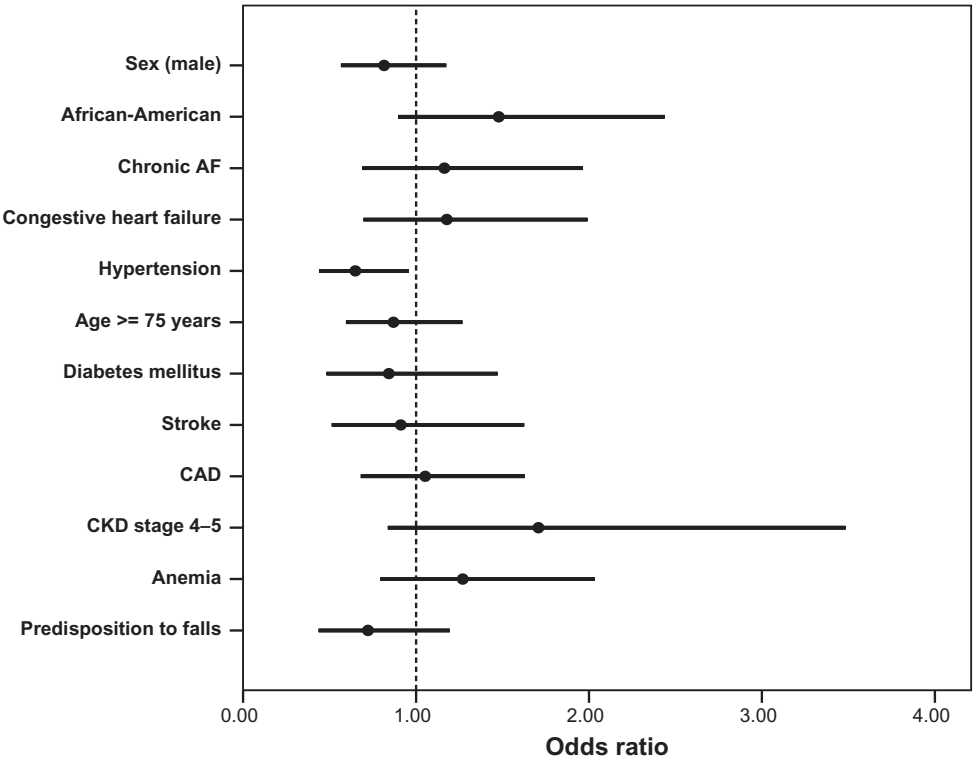

Figure 4 Forest plot of the predictors of warfarin interruptions.
Notes: Odds ratio with 95% confidence interval. Anemia = hemoglobin ≤ 10 mg/dL.
Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease (MDRD stages 4–5).

Table 3 Incidence rate of stroke and bleeding events by frequency of warfarin interruptions

	Events, n	Patient-years	Incidence density % (95% CI)	*P*-value
Stroke/TIA				0.01
No interruptions	27	1387	1.9 (1.3, 2.8)	
One interruption	13	570	2.3 (1.2, 3.9)	
≥two interruptions	25	702	3.6 (2.3, 5.3)	
Bleeding				0.86
No interruptions	27	1399	1.9 (1.3, 2.8)	
One interruption	10	583	1.7 (0.8, 3.2)	
≥two interruptions	13	773	1.7 (0.9, 2.9)	

Abbreviations: CI, confidence interval; TIA, transient ischemic attack.

started soon after diagnosis, warfarin-treated patients spent on average less than half of their follow-up time actually taking the medication. Over 25% of patients discontinued warfarin within 1 year, and less than half of these patients remained on warfarin at the conclusion of the study period. Furthermore, interruptions in warfarin use lasting on average nearly 1 year were common, affecting nearly one-third of those treated, and multiple interruptions were associated with more than twice the risk of stroke when compared to those with no interruptions in therapy. This increased risk appears despite those with multiple interruptions being younger, having lower stroke-risk scores, and similar estimates of TTR.

We also examined the quality of anticoagulation in our population as a proportion of TTR. Because we did not interpolate INR values beyond 45 days, over two-thirds of our person-time was classified as "unknown therapeutic range." When INRs could be interpolated, we found that only 47.3% of our patients' time was spent in therapeutic range, and less than one-quarter remained in therapeutic range for 60% or more of their exposure time. A recent study of 4408 atrial fibrillation patients demonstrated an inverse relationship between the interval between INR measurements and the observed TTR, with TTR decreasing from 48% to 41% as INR measurement intervals increased from 3 to 5 weeks.[31] Given that time classified as "unknown" in our analysis implies > 6 weeks between INR measurements, it is likely that with simple linear interpolation, the TTR in our population would be somewhat lower, though still similar to that seen in other studies performed in community-based settings.[24] These results highlight the significant proportion of untreated high-risk patients, the difficulty clinicians have in maintaining patients on warfarin once the decision is made to initiate anticoagulation, and the significant proportion of time patients remain unprotected from thrombotic events in actual clinical practice.

Few studies have looked specifically at interruptions or discontinuations in warfarin use and the consequences in terms of stroke and bleeding events. In one observational study of 4188 atrial fibrillation patients newly started on warfarin, over 26% discontinued within 1 year; with younger patients (≤65 years), those with poorer anticoagulation and those at lower stroke risk ($CHADS_2 = 0$) had the greatest risk of discontinuation.[23] Our 1-year discontinuation rate of 25% is similar to that seen in this and other studies where warfarin discontinuation ranges from 16% to 30% at 1 year.[32–34] Our study also confirms our current understanding concerning warfarin underuse in the community setting by examining a diverse set of actual clinical practices over a decade of time. Previous community-based studies report warfarin use in high-risk atrial fibrillation patients ranging from 39% to 92.3%, with the majority of studies reporting less than 60% usage.[15] Our results are consistent with these findings and serve to underscore the degree to which high-risk atrial fibrillation remains undertreated in actual clinical practice.

This study is limited by its retrospective design, restriction to a single health-care system, and its reliance on the completeness and accuracy of the data encoded within the EMR. Warfarin exposure was inferred using physician prescription history and INR values. Whether or not a patient actually filled a prescription was unknown, and it is likely that overall we overestimated exposure time. It is also likely that some patients were comanaged with external specialists. INRs obtained by these external practices would not always be captured in the EMR, resulting in gaps between measurements later classified as unknown TTR. The large proportion of unknown TTR limited its use in analyzing stroke and bleeding outcomes and as a result we used the frequency of warfarin interruptions as a surrogate for quality of anticoagulation. We did not, however, investigate the causes for these interruptions, and when TTR was known there was no significant difference in TTR ≥ 60% between groups. In addition, the limitation of this study to a single hospital system, despite its regional dominance, almost certainly underestimates the rate of stroke and bleeding events.

Given our limitations in measuring TTR, however, it is likely that the frequency of interruptions better reflects the overall quality of anticoagulation in this population, thus explaining its apparent impact on stroke risk.

In conclusion, this study supports previous findings that warfarin in actual practice is underutilized in a substantial portion of eligible atrial fibrillation patients. Furthermore, when warfarin is used, it is continued in less than half of these patients for less than half of their follow-up time. In addition, prolonged interruptions in anticoagulation are common in this population, and multiple interruptions are associated with over twice the risk of stroke when compared to those treated continuously. These findings highlight the substantial unmet need for adequate and consistent anticoagulation in this population.

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Disclosure

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Appendix

Appendix 1 Exclusion criteria data definitions

Criteria	Definition
Transient perioperative atrial fibrillation	An outpatient diagnosis of AF occurring within 30 days of an inpatient diagnosis of coronary artery bypass surgery (ICD-9 codes 36.10 to 36.19), pericardial surgery (ICD-9 codes 37.10 to 37.12, 37.31 to 37.33, or 37.40), or structural cardiac repair (ICD-9 codes 35.00 to 35.04, 35.31 to 35.39, 35.41 to 35.42, 35.50 to 35.56, 35.60 to 35.63, or 35.70 to 35.73)
Mitral or aortic valvular repair or replacement	An inpatient or office diagnosis of mitral stenosis or prosthetic heart valve (ICD-9 codes 394.0, 394.2, 396.0, 396.1, 396.8, V43.3, or V42.2) or mitral or aortic valve repair or replacement (ICD-9 codes 35.10 to 35.14 or 35.20 to 35.28)
Hyperthyroidism	Any of the following within 12 months before the index date: an inpatient or outpatient diagnosis of hyperthyroidism or thyrotoxicosis (ICD-9 codes 242.0 to 242.9)

Abbreviations: AF, atrial fibrillation; ICD-9, *International Classification of Diseases, Ninth Revision*.

Appendix 2 Potential barriers to warfarin use

Variable	Definition	Source
Prior GI/GU hemorrhage	Recent GI or GU hemorrhage recorded in the problem list or on hospital discharge (ICD-9 codes 578.x, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 535.x1, 530.82, 456.0, 456.2, 569.3, 596.7)	Office EMR Hospital discharges
Ethanol abuse	A history of ethanol abuse or related diagnoses (ICD-9 codes 291.0-2, 298.81, 303.x, 305.0x, 571.0-3, 535.3) prior to the index date recorded in the problem list or indicated in office notes on CAGE assessment or social history	Office EMR Hospital discharges
Predisposition to falls	ICD-9 codes recorded in the problem list or on hospital discharge of 290.x-294.x, 331.0, 331.1, 333.4, 345.x, 347, 458.0, 780.2, 780.3, E880-888	Office EMR Hospital discharges
Perceived barriers to compliance	ICD-9 codes recorded in the problem list or on hospital discharge of 295.x-298.x, V60.0-V60.4, V15.81	Office EMR Hospital discharges
Cirrhosis/hepatitis	ICD-9 codes recorded in the problem list or on hospital discharge of 070.2–070.9, 570, 571.x, 572.2, 572.3, 572.4, 572.8, 573.x or an elevated aspartate transaminase or alanine transaminase value ($\geq 2 \times$ normal)	Office EMR Hospital discharges Lab database
Renal insufficiency	A diagnosis of renal disease (ICD-9 codes 042.9, 285.2, 403.x, 404.x, 572.4, 582.x, 583.x, 584.5–584.9, 585.x, 753.13, 799.9, 866.0) entered by a physician prior to the index in the problem list or evidence of chronic kidney disease stage 4 or 5 by estimated glomerular filtration rate (calculated by Modification of Diet in Renal Disease equation)	Office EMR Hospital discharges Lab database

Abbreviations: GI, gastrointestinal; GU, genitourinary; EMR, electronic medical record; ICD-9, *International Classification of Diseases, Ninth Revision*.

Appendix 3 Predictors of stroke and their definitions

Variable	Definition	Source
Age	Calculated age of patient at time of the index visit using index date and date of birth	Office EMR
Age ≥ 75	Age at index date expressed as a dichotomous variable (1 = age ≥ 75 years, 0 = age < 75 years	Office EMR
Congestive heart failure	A diagnosis of heart failure recorded prior to or on the index date in the office-record problem list or evidence of a hospital admission with a principal diagnosis of heart failure (ICD-9 codes 428.x)	Office EMR Hospital discharges
Hypertension	A diagnosis of hypertension prior to the index date entered by a physician in the office-record problem list or at least two serial blood pressure measures > 140/90	Office EMR
Diabetes	A diagnosis of diabetes mellitus (ICD-9-CM codes 250.xx) prior to the index entered by a physician in the office-record problem list or an active oral hypoglycemic medication or insulin on the office medication list	Office EMR
Coronary heart disease	A diagnosis entered by a physician in the problem list or a hospital discharge with a principal ICD-9 code of 410, 411, 413 – 414, 429.2 prior to index	Office EMR Hospital discharges
Stroke or transient ischemic attack	A hospital discharge with a principal ICD-9 code of 430, 431, 433-436 prior to index. Hospitalizations with ICD-9 codes 433.x-436.x lasting less than 48 hours and associated carotid endarterectomy will be excluded	Hospital discharges
$CHADS_2$	A stroke risk score using five of the above variables. The total score is the sum of the following factors: congestive heart failure = 1, hypertension = 1, age ≥ 75 years = 1, diabetes mellitus = 1, and prior stroke or transient ischemic attack = 2	Office EMR Hospital discharges

Abbreviations: EMR, electronic medical record; ICD-9, *International Classification of Diseases, Ninth Revision*.