ORIGINAL RESEARCH

Stroke and Bleeding Risk Associated With Antithrombotic Therapy for Patients With Nonvalvular Atrial Fibrillation in Clinical Practice

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***Background*—**The quality of antithrombotic therapy for patients with nonvalvular atrial fibrillation during routine medical care is often suboptimal. Evidence linking stroke and bleeding risk with antithrombotic treatment is limited. The purpose of this study was to evaluate the associations between antithrombotic treatment episodes and outcomes.

***Methods and Results*—**A retrospective longitudinal observational cohort study was conducted using patients newly diagnosed with nonvalvular atrial fibrillation with 1 or more stroke risk factors ($CHADS_2 \geq 1$) in Kaiser Permanente Southern California between January 1, 2006 and December 31, 2011. A total of 1782 stroke and systemic embolism (SE) and 3528 major bleed events were identified from 23 297 patients during the 60 021 person-years of follow-up. The lowest stroke/SE rates and major bleed rates were observed in warfarin time in therapeutic range (TTR) ≥55% episodes (stroke/SE: 0.87 [0.71 to 1.04]; major bleed: 4.91 [4.53 to 5.28] per 100 person-years), which was similar to the bleed rate in aspirin episodes (4.95 [4.58 to 5.32] per 100 person-years). The warfarin TTR ≥55% episodes were associated with a 77% lower risk of stroke/SE (relative risk=0.23 [0.18 to 0.28]) compared to never on therapy; and the warfarin TTR <55% and on-aspirin episodes were associated with a 20% lower and with a 26% lower risk of stroke/SE compared to never on therapy, respectively. The warfarin TTR <55% episodes were associated with nearly double the risk of a major bleed compared to never on therapy (relative risk=1.93 [1.74 to 2.14]).

***Conclusions*—**Continuation of antithrombotic therapy as well as maintaining an adequate level of TTR is beneficial to prevent strokes while minimizing bleeding events. **(*J Am Heart Assoc*. 2015;4:e001921 doi: 10.1161/JAHA.115.001921)**

Key Words: antithrombotic • atrial fibrillation • bleeding • outcomes research • stroke

Nonvalvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia, affecting ≈5.2 million people in the United States.[1] The rate of ischemic strokes among NVAF patients averages 5% per year, 2 to 7 times higher than people without NVAF.[2] Clinical guidelines recommend oral anticoagulants for NVAF patients to prevent thromboembolism and suggest maintaining the target international normalized ratio (INR) for patients treated with warfarin.[3,4]

The quality of antithrombotic therapy (either anticoagulant or antiplatelet) during routine medical care is often suboptimal. Previous studies showed that 30% to 40% of those at high risk for stroke fail to receive recommended anticoagulant therapy[5–8] and even after they start on warfarin therapy, ≈30% of patients discontinued their warfarin within 1 year.[9,10] Also, the quality of warfarin therapy is often suboptimal; the average of time in therapeutic range (TTR) of INR values ranged from 51% to 63% based on the management setting in the United States.[11]

Understanding outcomes of antithrombotic treatment patterns in a real-world setting is critical; however, the evidence is still unclear. Over-the-counter aspirin use is usually missing in an observational data set, and the outcomes associated with TTR levels in clinical practice have not been extensively studied. Several analyses of randomized controlled trials[12–16] and some observational studies[17,18] have examined the relationship between TTR and clinical events. In general, these studies demonstrated the decreased stroke rates in higher TTR, whereas the relationship between the higher TTR and bleeding risk has been more variable.[19]

The purpose of this study was to evaluate the associations between different antithrombotic treatments—warfarin TTR ≥55%, warfarin TTR <55%, off warfarin, on aspirin, off aspirin, and never on antithrombotic therapy—and their clinical

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outcomes (strokes, systemic embolism [SE], and major bleeding) for moderate stroke-risk patients (congestive heart failure, hypertension, age ≥75, diabetes, stroke/transient ischemic attack, $CHADS_2$ ≥1) with NVAF in clinical practice.

Methods

Study Design

A retrospective longitudinal observational cohort study was conducted considering multiple antithrombotic treatments for each individual. Patients may have had multiple treatment and nontreatment times during the entire follow-up period (eg, stop therapy, switch therapy, and restart therapy). The dynamics of treatment patterns and outcomes associated with them were captured in a longitudinal analysis.

Study Setting

Study population was identified from Kaiser Permanente Southern California (KPSC). KPSC is a nonprofit, integrated healthcare delivery organization with a membership of over 3.6 million people in Southern California. KPSC provides integrated, comprehensive medical services through its own facilities, which include 14 hospitals, >200 outpatient facilities, and a centralized laboratory. All aspects of care and interaction with the healthcare delivery system are captured in a continuously updated electronic medical record (EMR) system. Over 95% of the patients receiving warfarin treatment in KPSC are participants of anticoagulation clinics led by pharmacists. Each encounter (mostly telephone counseling) at an anticoagulation clinic is stored in the EMR system.

Study Cohort

Patients newly diagnosed with atrial fibrillation (≥2 serial International Classification of Diseases, Ninth Revision Clinical Modification [ICD-9-CM] of 427.31 ≥30 days apart) in outpatient visit or hospital records were identified between January 1, 2006 and December 31, 2011. The first diagnosis date was defined as the index date and patients were followed until the first outcomes of interest, end of enrollment, death, or December 31, 2012, whichever occurred first. Individuals who had a history of atrial fibrillation diagnosis, ablation, cardioversion, warfarin prescription, or an anticoagulation clinic visit during 12 months prior to the index date were excluded to ensure that only newly diagnosed NVAF patients were captured. Patients <18 years old at index, without continuous health-plan membership or drug benefit during the 12 months prior to the index date (gaps of ≤30 days were treated as continuous membership), evidence of pregnancy at any point during the entire follow-up period, and individuals who had valvular diseases, valvular repair, or replacement 12 months prior to the index date were also excluded. In the final study cohort, we excluded patients on novel oral anticoagulation agents (dabigatran and rivaroxaban: N=101) due to small sample size, and patients who only had 1 warfarin prescription but were not followed by an anticoagulation clinic (N=133), since it would be difficult to confirm these patients were taking warfarin due to lack of monitoring. The analyses were conducted for patients with at least 1 or more major risk factors for stroke ($CHADS_2$ ≥1). The current study was reviewed and approved by the KPSC Institutional Review Board. Informed consent was waived due to the retrospective observational nature of this study.

Antithrombotic Therapy Definitions

Warfarin treatment (TTR ≥55%, TTR <55%, off warfarin episodes)

We defined warfarin treatment episodes using prescriptions, INR lab measurements, and anticoagulation clinic data. The start date of a warfarin episode was defined as the first warfarin prescription date, and the end date of the episode was defined as the earliest date with one for the following: (1) date of discharge from the anticoagulation clinic; or (2) the most recent covered date (last refill date plus days' supply) plus additional 80 days of grace period to incorporate interpersonal variability of warfarin dosage use; or (3) INR measurement date plus 80 days of grace period (regular INR measurement intervals at KPSC [8 weeks] and around 4 weeks of additional period[20]) from the date of discharge. Previous literature[9,20] applied 30 days of grace period at the end of a prescription because patients may be instructed to take half-doses of warfarin.[20] Applying a similar concept, we determined 80 days of grace period since this is a mean warfarin days' supply at KPSC.

TTR was calculated using the linear interpolation method by Rosendaal et al[21] expressed as a percentage of observation time, which in our study we defined as each warfarin treatment episode. We considered the INR range of 2 to 3 as therapeutic. INR tests performed during hospitalization or INR gaps >80 days were not interpolated. Based on TTR, we stratified patients into 2 different groups (warfarin TTR ≥55%, warfarin TTR <55%). There is no consensus in terms of appropriate TTR cutoff. The 55% threshold was selected a priori since this level is the lower bound of reported means from previous clinical trials and large observational studies.[22,23] The 55% threshold may be understood as the initial cutoff for poor control. Stratified analyses were conducted to investigate the outcomes at the different TTR levels based on the distribution of the data. No treatment time after warfarin use was considered "off warfarin" period.

Aspirin-only treatment (on aspirin, off aspirin episodes)

Low-dose aspirin (75 to 325 mg) use in the EMR, chart notes, and prescription data were searched for the entire nonwarfarin time. We built a natural language processing algorithm[24–26] to search for low-dose aspirin use information, and ≥1 evidence of aspirin use was considered as being on aspirin. Chart notes (5339) from 100 patients' records were randomly selected and manually reviewed to validate the algorithm. The algorithm achieved 95.5% sensitivity and 98.9% specificity. The positive predictive value was 93.0% with negative predictive value of 99.3%. We applied ±180 days criteria for the first and the last evidence of aspirin use and assumed patients were on aspirin during this period. The nontreatment time after aspirin use was considered as "off aspirin" period.

No therapy ("never on therapy" episode)

Some patients were never on warfarin or aspirin therapy. Thus, the entire follow-up time for this patient group was considered as "never on therapy" episode. There was another group of patients who started warfarin or aspirin therapy after their index date. The time between the index date to the first use of warfarin or aspirin was considered as a "never on therapy" period since they were not on a therapy until their first medication.

Outcomes Definition

The outcomes of interest were stroke and/or SE (stroke/SE) and major bleed. Primary hospital discharge diagnoses of stroke (ICD-9-CM of 430, 431, 433.xx, 434.xx, 436.xx)

Table 1. Definition of Outcomes

	ICD-9-CM or CPT Codes
Stroke/systemic embolism	All stroke or systemic embolism
Stroke	Primary hospital discharge record 430, 431, 433.xx, 434.xx, 436.xx
Systemic embolism	Primary hospital discharge record 444.0, 444.1, 444.2x, 444.8x, 444.9, 557.x, 593.81
Bleeding events	
Major bleeding	A bleeding event will be defined as major if it was an intracranial bleed or any other bleed that was associated with the following: inpatient care, blood transfusion of 2 or more units of whole blood or red blood cells, decreased hemoglobin or hematocrit of 2 g/dL or more, physician-guided medical or surgical treatment, or death*
Intracranial hemorrhage	Primary or secondary hospital discharge record 432.x Exclude intracranial hemorrhage associated with a concomitant discharge diagnosis of major trauma (ICD-9-CM codes 852.1, 852.3, 852.5, and 853.1)
Gastrointestinal bleeding	Primary hospital discharge record 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.31, 532.4x, 532.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1, 537.83, 537.84, 537.89, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.69, 569.85, 577.8, 578.x, 580.9, 596.7, 596.8, 599.7x
Other bleeding (intraspinal, intraocular, pericardial, intra-articular, intramuscular, etc)	Primary hospital discharge record 255.41, 423.0, 455.2, 455.5, 455.8, 456.0, 456.2. 456.8, 459.0, 719.1x, 784.7, 784.8, 785.59, 786.3, 853.0x
Others	To define major bleeding
Physician-guided medical or surgical treatment*	From primary or secondary hospital discharge record CPT codes: 10140, 10160, 11740, 21501, 21502, 23030, 23930, 25028, 26990, 27301, 27603, 30000, 30020, 30901, 30903, 30905, 30906, 31238, 32110, 32654, 32658, 33020, 40800, 40801, 41000, 41005, 41006, 41007, 41008, 41009, 41015, 41016, 41017, 41018, 41800, 42960, 42961, 42962, 42970, 42971, 42972, 43227, 43255, 43460, 43501, 44366, 44378, 44391, 45317, 45334, 45382, 46614, 47350, 47360, 47361, 47362, 52606, 54700, 57023, 57180, 61108, 61154, 61156, 61312, 61313, 61314, 61315, 61322, 61323, 65930, 69000, 69005, 91100 ICD-9-CM procedure codes: 44.43, 44.44, 44.49

CPT indicates Current Procedural Terminology; ICD-9-CM, International Classification of Diseases, Ninth Revision Clinical Modification.
*Death information may not be complete since there is a 1-year delay in receiving death information from California State death records, and federal sources.

and/or SE (444.0, 444.1, 444.2x, 444.8x, 444.9, 557.x, 593.81) was defined as an outcome. Major bleed was defined as an intracranial bleed or any other bleed (gastrointestinal, intraspinal, intraocular, pericardial, intra-articular, intramuscular bleed) that was associated with an inpatient care visit; blood transfusion of 2 or more units of whole blood or red blood cells; decreased hemoglobin 2 g/dL or more; physician-guided medical or surgical treatment; or death (Table 1). Decreased hemoglobin was identified by searching 7 days before and 7 days after the bleed diagnosis codes and determining nadir hemoglobin level. The highest hemoglobin level before the nadir level was considered as a baseline value and was compared with the nadir level. A decrease in 2 g/dL or more was considered a major hemorrhage according to the definition published by the International Society on Thrombosis and Hemostatis.[27]

Statistical Analyses

Patient-level baseline characteristics were investigated and descriptive statistics were reported to examine differences among each treatment option (warfarin use, aspirin only, and no therapy). The crude rate of stroke/SE and major bleeding (number of events per 100 person-years [PY]) were evaluated for each treatment episode. Longitudinal multivariable analyses using generalized estimating equations (logit link, Poisson distribution) were conducted considering interindividual correlations. Patient demographics (age, gender, race/ethnicity), body mass index, baseline comorbidities (peripheral vascular disease, cirrhosis, cardiac myopathy, dementia), history of bleed, myocardial infarction, or fall, and baseline medication use (periprocedural anticoagulation, antiarrhythmic medications, clopidogrel, ticlopidine, prasugrel, ticagrelor, heart rate control medications, statin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) were considered as covariates. *P*-value <0.2 in the univariate analysis, and other clinically relevant covariates were included in the multivariable regression model. The final multivariable model was created by applying a backward model selection procedure that retained those covariates with $P<0.05$. Other clinically relevant covariates that were not significant were forced into the final model as needed. We used key risk factors such as age, congestive heart failure, hypertension, diabetes, stroke/transient ischemic attack, and major bleed as time-varying covariates. Relative risks (RR) with 95% CI were reported from the multivariable analyses. Subgroup analyses were conducted based on the baseline $CHADS_2$ scores (1, 2, ≥3). The outcomes based on TTR distribution were investigated.

Results

A total of 23 297 patients with $CHADS_2$ ≥1 were included in the study. A cohort diagram is shown in Figure 1. Data were censored at the first occurrence of each outcome of interest; a total of 60 021 PY for stroke/SE outcomes, and 56 760 PY for major bleed outcomes were identified in this study. Among the population, 47.5% had at least 1 warfarin prescription, 29.0% had evidence of aspirin use only, and 23.5% did not receive any antithrombotic therapy. Mean (SD) age of the population was 74.9 (11.1) years, and 47.7% were female. The median TTR for the warfarin group was 59%. Baseline characteristics are shown in Table 2. Baseline differences were found among 3 different treatment groups (warfarin, aspirin only, and no therapy). Mean (SD) age of the aspirin-only group was higher compared to warfarin users (77.6 [10.8] for aspirin versus 73.1 [10.3] for warfarin) and a higher percentage of patients age ≥85 was found in the aspirin-only group. Warfarin users had higher rates of comorbidities: hypertension, diabetes, and stroke/transient ischemic attack compared to the aspirin-only group, whereas the aspirin-only and no-therapy groups had higher rates of

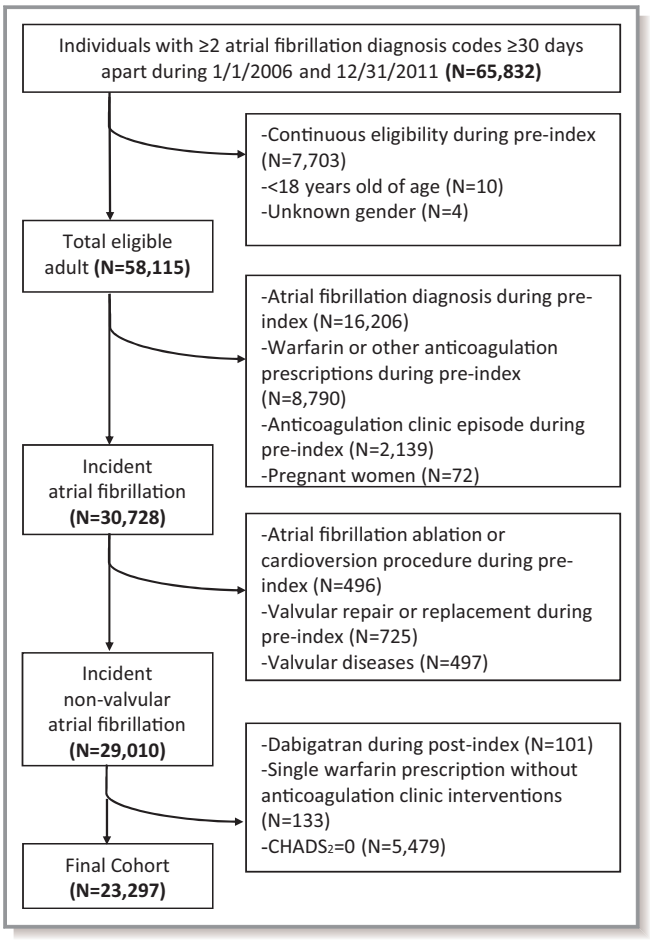

Figure 1. Study cohort diagram.

Table 2. Baseline Characteristics

Variables	Warfarin (N=11 079)	Aspirin Only (N=6746)	No Therapy (N=5472)	Total (N=23 297)
Age, mean (SD)	73.1 (10.3)	77.6 (10.8)	75.0 (12.3)	74.9 (11.1)
Age category, y, N (%)				
Age <65	2172 (19.6)	877 (13)	1080 (19.7)	4129 (17.7)
Age 65 to 74	3219 (29.1)	1322 (19.6)	1202 (22)	5743 (24.7)
Age 75 to 84	4421 (39.9)	2600 (38.5)	1893 (34.6)	8914 (38.3)
Age ≥85	1267 (11.4)	1947 (28.9)	1297 (23.7)	4511 (19.4)
Gender, N (%)				
Female	5161 (46.6)	3291 (48.8)	2665 (48.7)	11 117 (47.7)
Charlson Comorbidity Score, mean (SD)	2.4 (3.04)	2.6 (3.30)	2.5 (3.37)	2.5 (3.20)
Charlson Comorbidity Score category, N (%)				
0	4769 (43)	3049 (45.2)	2559 (46.8)	10 377 (44.5)
1 to 3	3281 (29.6)	1699 (25.2)	1356 (24.8)	6336 (27.2)
4 or more	3029 (27.3)	1998 (29.6)	1557 (28.5)	6584 (28.3)
Comorbid conditions or event, N (%)				
Congestive heart failure	1953 (17.6)	1321 (19.6)	1011 (18.5)	4285 (18.4)
Hypertension	9688 (87.4)	5615 (83.2)	4548 (83.1)	19 851 (85.2)
Diabetes mellitus	3608 (32.6)	2016 (29.9)	1583 (28.9)	7207 (30.9)
Stroke/transient ischemic attack	407 (3.7)	160 (2.4)	202 (3.7)	769 (3.3)
Peripheral vascular disease	772 (7)	593 (8.8)	408 (7.5)	1773 (7.6)
Myocardial infarction	368 (3.3)	283 (4.2)	172 (3.1)	823 (3.5)
Cardiomyopathy	708 (6.4)	419 (6.2)	297 (5.4)	1424 (6.1)
Liver cirrhosis	41 (0.4)	49 (0.7)	84 (1.5)	174 (0.7)
Dementia	69 (0.6)	149 (2.2)	128 (2.3)	346 (1.5)
Bleeding	742 (6.7)	602 (8.9)	531 (9.7)	1875 (8)
Fall	100 (0.9)	151 (2.2)	93 (1.7)	344 (1.5)
$CHADS_2$ scores, N (%)				
1	3773 (34.1)	2095 (31.1)	2031 (37.1)	7899 (33.9)
2	4667 (42.1)	2764 (41)	2069 (37.8)	9500 (40.8)
3 or more	2639 (23.8)	1887 (28)	1372 (25.1)	5898 (25.3)
Other pharmacologic treatment, N (%)				
Heart rate control	7520 (67.9)	4504 (66.8)	3495 (63.9)	15 519 (66.6)
Antiarrhythmic medications	294 (2.7)	322 (4.8)	222 (4.1)	838 (3.6)
Secondary prevention of cardiovascular disease	8738 (78.9)	5076 (75.2)	3864 (70.6)	17 678 (75.9)
Other antiplatelet agents*	805 (7.3)	525 (7.8)	459 (8.4)	1789 (7.7)
Periprocedural anticoagulation	1037 (9.4)	715 (10.6)	527 (9.6)	2279 (9.8)
Median time in therapeutic range (INR 2 to 3) (%)	59%	—	—	—

INR indicates international normalized ratio.
*Clopidogrel, ticlopidine, prasugrel, ticagrelor use.

congestive heart failure, myocardial infarction, and bleeding. A higher percentage of patients with $CHADS_2$ ≥2 was found in the aspirin group compared to the warfarin or no-therapy groups.

A total of 1782 stroke/SE events occurred during the follow-up period. The lowest stroke/SE rates (95% CI) were observed in the warfarin TTR ≥55% episodes (0.87 [0.71 to 1.04] per 100 PY) (Table 3). The stroke/SE event rates from

Table 3. Crude Rate of Stroke/Systemic Embolism and Major Bleed Events

	Warfarin			Aspirin Only		No Therapy	
	Warfarin TTR ≥55%	Warfarin TTR <55%	Off Warfarin	On Aspirin	Off Aspirin	Never on Therapy	Total
Stroke/SE							
Number of episode (total person-years)	5960 (12 928)	5292 (5603)	10 092 (3679)	11 794 (15 029)	5219 (5329)	15 603 (17 453)	53 960 (60 021)
Events per 100 person-years (95% CI)							
All patients (N=23 297)	0.87 (0.71 to 1.04)	3.23 (2.76 to 3.70)	4.38 (3.70 to 5.05)	3.11 (2.83 to 3.39)	3.81 (3.29 to 4.33)	3.76 (3.48 to 4.05)	2.97 (2.83 to 3.11)
Ischemic stroke	0.64 (0.50 to 0.78)	2.52 (2.10 to 2.93)	2.80 (2.26 to 3.34)	2.64 (2.38 to 2.90)	3.17 (2.69 to 3.65)	3.04 (2.78 to 3.30)	2.37 (2.25 to 2.50)
Hemorrhagic stroke	0.09 (0.09 to 0.14)	0.29 (0.15 to 0.43)	1.14 (0.80 to 1.49)	0.13 (0.07 to 0.18)	0.30 (0.15 to 0.45)	0.29 (0.21 to 0.37)	0.26 (0.22 to 0.30)
SE	0.15 (0.08 to 0.21)	0.43 (0.26 to 0.61)	0.43 (0.22 to 0.65)	0.34 (0.25 to 0.43)	0.34 (0.18 to 0.49)	0.43 (0.33 to 0.53)	0.34 (0.29 to 0.38)
$CHADS_2$=1 (N=7899)	0.68 (1.45 to 0.92)	1.78 (1.16 to 2.40)	1.97 (1.27 to 2.68)	2.06 (1.65 to 2.47)	2.09 (1.44 to 2.75)	1.73 (4.13 to 2.03)	1.62 (1.46 to 1.79)
$CHADS_2$=2 (N=9500)	1.05 (0.78 to 1.32)	3.61 (2.84 to 4.37)	5.53 (4.28 to 6.78)	3.29 (2.85 to 3.73)	4.05 (3.22 to 4.88)	3.84 (3.37 to 4.31)	3.15 (2.93 to 3.37)
$CHADS_2$=3 or higher (N=5898)	0.84 (0.48 to 1.20)	4.42 (3.34 to 5.50)	6.98 (5.15 to 8.81)	4.06 (3.42 to 4.69)	5.99 (4.62 to 7.37)	7.93 (6.99 to 8.86)	4.85 (4.48 to 5.23)
Major bleed							
Number of episode (total person-years)	6096 (13 226)	5354 (5687)	8836 (2667)	10 894 (14 004)	4423 (4514)	15 162 (16 662)	50 765 (56 760)
Events per 100 person-years (95% CI)							
All patients (N=23 297)	4.91 (4.53 to 5.28)	12.33 (11.41 to 13.24)	9.56 (8.39 to 10.73)	4.95 (4.58 to 5.32)	5.23 (4.56 to 5.89)	5.97 (5.59 to 6.34)	6.22 (6.01 to 6.42)
ICH	0.21 (0.13 to 0.29)	0.44 (0.27 to 0.61)	1.65 (1.16 to 2.14)	0.16 (0.10 to 0.23)	0.31 (0.15 to 0.47)	0.35 (0.26 to 0.44)	0.34 (0.29 to 0.39)
GI bleed	2.98 (2.68 to 3.27)	8.42 (7.67 to 9.18)	6.30 (5.35 to 7.25)	3.73 (3.41 to 4.05)	3.74 (3.18 to 4.31)	4.39 (4.07 to 4.71)	4.34 (4.17 to 4.51)
Other bleed	1.72 (1.49 to 1.94)	3.46 (2.98 to 3.95)	1.61 (1.13 to 2.09)	1.05 (0.88 to 1.22)	1.17 (0.86 to 1.49)	1.22 (1.06 to 1.39)	1.53 (1.43 to 1.64)
$CHADS_2$=1 (N=7899)	3.80 (3.25 to 4.34)	10.43 (8.94 to 11.92)	5.47 (4.10 to 6.85)	2.93 (2.39 to 3.47)	2.16 (1.33 to 2.98)	4.26 (3.78 to 4.74)	4.39 (4.10 to 4.68)
$CHADS_2$=2 (N=9500)	5.07 (4.49 to 5.66)	12.38 (10.96 to 13.79)	10.76 (8.72 to 12.80)	4.85 (4.28 to 5.41)	5.31 (4.23 to 6.38)	6.43 (5.80 to 7.06)	6.41 (6.08 to 6.74)
$CHADS_2$=3 or higher (N=5898)	6.61 (5.62 to 7.59)	14.52 (12.60 to 16.44)	15.59 (12.31 to 18.86)	6.89 (6.10 to 7.67)	7.52 (6.16 to 8.88)	8.75 (7.74 to 9.75)	8.53 (8.04 to 9.01)

GI indicates gastrointestinal; ICH, intracranial hemorrhage; SE, systemic embolism; TTR, time in therapeutic range.

the warfarin TTR <55% episodes were similar (3.23 [2.76 to 3.70] per 100 PY) compared to the event rates during episodes of aspirin use (3.11 [2.83 to 3.39] per 100 PY). Higher occurrences of stroke/SE were observed during periods of no treatment (off warfarin, off aspirin, and never on therapy). The highest stroke/SE rates were found during

Table 4. Factors Associated With Stroke/SE

Variables	Thromboembolic Events			
	Relative Risk	95% CI		*P* Value
Time-varying antithrombotic treatment				
Warfarin TTR ≥55% (vs never on therapy)	0.23*	0.18	0.28	<0.0001
Warfarin TTR <55% (vs never on therapy)	0.80*	0.67	0.95	0.0098
Off warfarin (vs never on therapy)	1.22*	1.01	1.48	0.0358
On aspirin (vs never on therapy)	0.74*	0.65	0.83	<0.0001
Off aspirin (vs never on therapy)	0.96	0.82	1.13	0.6466
Time-invariant factors				
Female (vs male)	1.34*	1.22	1.48	<0.0001
Race				
Black (vs white)	1.51*	1.29	1.76	<0.0001
Hispanic (vs white)	1.16*	1.00	1.34	0.0442
Asian and others (vs white)	1.05	0.86	1.29	0.605
Baseline peripheral vascular disease (yes vs no)	1.24*	1.05	1.46	0.0112
Baseline smoking status				
Smoker (vs nonsmoker)	1.15	0.94	1.40	0.1768
Unknown (vs nonsmoker)	1.57*	1.37	1.80	<0.0001
Baseline CCI				
CCI 1 to 3 (vs CCI=0)	1.34*	1.19	1.51	<0.0001
CCI ≥4 (vs CCI=0)	1.27*	1.11	1.45	0.0006
Time-varying factors				
Time-varying age group, y				
Age 65 to 74 vs age <65	1.32*	1.09	1.59	0.0043
Age 75 to 84 vs age <65	2.15*	1.81	2.56	<0.0001
Age ≥85 vs age <65	3.15*	2.63	3.78	<0.0001
Time-varying congestive heart failure (yes vs no)	1.07	0.94	1.22	0.2959
Time-varying diabetes (yes vs no)	1.15*	1.03	1.29	0.0105
Time-varying hypertension (yes vs no)	1.25*	1.08	1.44	0.0023
Time-varying stroke/transient ischemic attack (yes vs no)	3.78*	3.16	4.53	<0.0001
Recent bleeding (for stroke/SE events only)	0.72*	0.58	0.89	0.0025

Results from a single multivariable regression model. CCI indicates Charlson Comorbidity Index; SE, systemic embolism; TTR, time in therapeutic range.
*Statistically significant.

the off-warfarin therapy episodes (4.38 [3.70 to 5.05] per 100 PY). The majority of the total stroke/SE events were from ischemic stroke (79.9%) and 8.7% were from hemorrhagic stroke.

A total of 3528 major bleed events occurred during the follow-up period. The lowest major bleed rates (95% CI) were also found during warfarin TTR ≥55% episodes (4.91 [4.53 to 5.28] per 100 PY), and these were similar to the rates observed during episodes of aspirin use (4.95 [4.58 to 5.32] per 100 PY) (Table 3). Bleeding rates were the highest in warfarin TTR <55% episodes (12.33 [11.41 to 13.24] per 100 PY), followed by off-warfarin episodes (9.56 [8.39 to 10.73] per 100 PY). A large proportion (69.8%) of major bleeds was gastrointestinal bleeds and 5.5% were from intracranial hemorrhages.

When controlling for other factors and individual correlations due to an individual patient having multiple episodes, warfarin TTR ≥55% episodes were associated with a 77% lower risk of stroke/SE (adjusted RR [95% CI]=0.23 [0.18 to 0.28]) compared to never on therapy episodes, whereas warfarin TTR <55% and on-aspirin episodes were associated with a 20% lower risk and with a 26% lower risk of stroke/SE compared

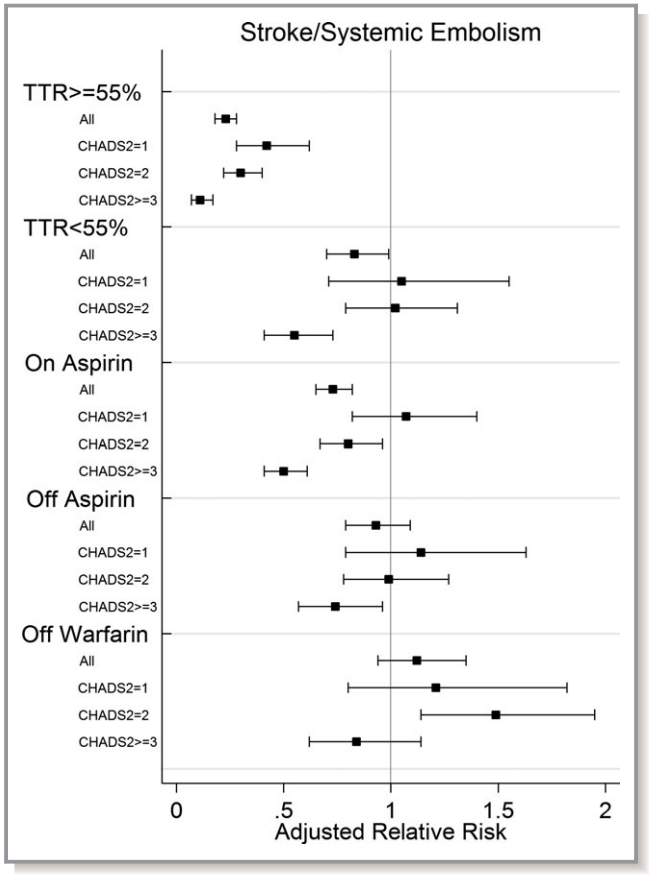

Figure 2. Adjusted relative risks (95% CI) of stroke/systemic embolism for antithrombotic treatment (vs never on therapy). TTR indicates time in therapeutic range.

to never on therapy episodes, respectively (Table 4 and Figure 2). The stroke/SE risks from off-aspirin episodes were not statistically different from never on therapy episodes; however, a 22% higher risk of stroke/SE was found from off-warfarin episodes compared to never on therapy episodes (RR=1.22 [1.01 to 1.48]). Other significant factors associated with stroke/SE included older age, female gender, black or Hispanic race, having diabetes, hypertension, previous stroke/transient ischemic attack, peripheral vascular events, higher comorbidity score, and no experiences of recent major bleed.

Controlling for other factors, warfarin TTR <55% was associated with nearly twice the risk of a major bleed compared to never being on therapy (adjusted RR=1.93 [1.74 to 2.14]) (Table 5, Figure 3). However, warfarin TTR ≥55% episodes were associated with a reduced risk of major bleed compared to never on therapy episodes (RR=0.84 [0.76 to 0.93]). Similar risk was observed from the on-aspirin or off-aspirin episodes. Increased risk of bleed was observed in the off-warfarin compared to never on therapy episodes (RR=1.54 [1.33 to 1.79]). Many factors associated with a major bleed were the same as those associated with stroke/SE including

Table 5. Factors Associated With Major Bleed

Variables	Bleeding Events			
	Relative Risk	95% CI		*P* Value
Time-varying antithrombotic treatment				
Warfarin TTR ≥55% (vs never on therapy)	0.84*	0.76	0.93	0.001
Warfarin TTR <55% (vs never on therapy)	1.93*	1.74	2.14	<0.0001
Off warfarin (vs never on therapy)	1.54*	1.33	1.79	<0.0001
On aspirin (vs never on therapy)	0.72*	0.65	0.80	<0.0001
Off aspirin (vs never on therapy)	0.80*	0.69	0.93	0.0028
Time-invariant factors				
Female (vs male)	0.72*	0.67	0.77	<0.0001
Race				
Black (vs white)	1.28*	1.14	1.44	<0.0001
Hispanic (vs White)	1.16*	1.05	1.28	0.0038
Asian and others (vs white)	1.15*	1.01	1.31	0.0412
Baseline bleed (yes vs no)	1.95*	1.76	2.16	<0.0001
Baseline periprocedural anticoagulation (yes vs no)	1.21*	1.08	1.37	0.0017
Baseline CCI				
CCI 1 to 3 (vs CCI=0)	1.31*	1.20	1.43	<0.0001
CCI ≥4 (vs CCI=0)	1.93*	1.76	2.12	<0.0001
Time-varying factors				
Time-varying age group				
Age 65 to 74 vs age <65	1.46*	1.30	1.65	<0.0001
Age 75 to 84 vs age <65	1.65*	1.46	1.86	<0.0001
Age ≥85 vs age <65	2.20*	1.92	2.52	<0.0001
Time-varying $CHADS_2$=2 (yes vs no)	1.15*	1.05	1.27	0.003
Time-varying $CHADS_2$ ≥3 (yes vs no)	1.20*	1.07	1.34	0.0017
Recent stroke/SE	0.61*	0.49	0.74	<0.0001

Results from a single multivariable regression model. CCI indicates Charlson Comorbidity Index; SE, systemic embolism; TTR, time in therapeutic range.
*Statistically significant.

older age, black or Hispanic race, and higher comorbidity score (Tables 4 and 5). Being male, having congestive heart failure, baseline bleed, and no experience of recent stroke/SE were also associated with an increased risk of major bleed.

Subgroup analyses showed that stroke/SE as well as major bleeding events were increased in higher $CHADS_2$ risk categories (stroke/SE event rates=1.62 per 100 PY for $CHADS_2$=1, 3.15 for $CHADS_2$=2, 4.85 for $CHADS_2$ ≥3;

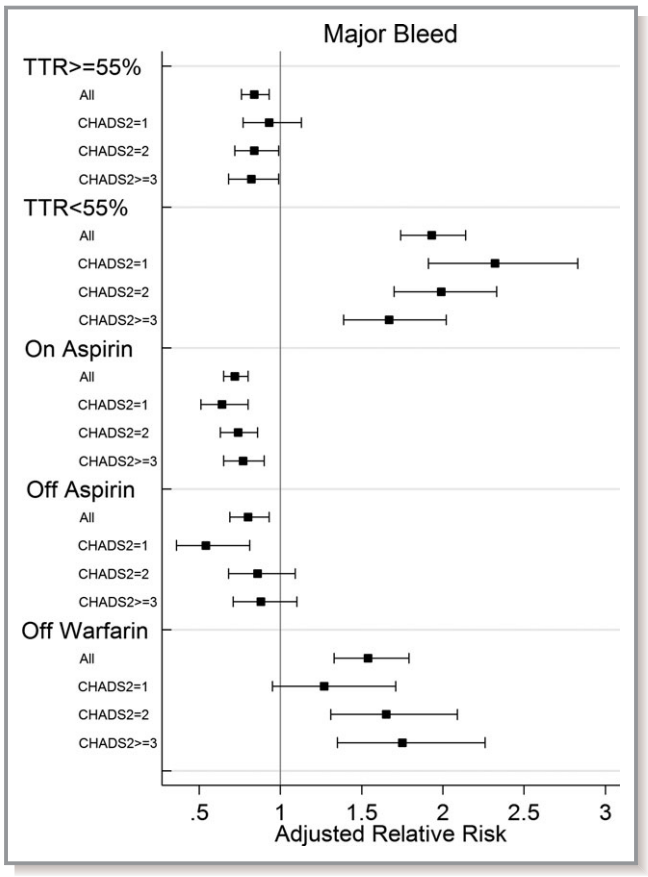

Figure 3. Adjusted relative risks (95% CI) of major bleed for antithrombotic treatment (vs never on therapy). TTR indicates time in therapeutic range.

major bleed event rates=4.39 for $CHADS_2$=1, 6.41 for $CHADS_2$=2, 8.53 for $CHADS_2$ ≥3) (Table 3). The antithrombotic treatment effect was relatively consistent among different $CHADS_2$ risk groups (Figures 2 and 3). A greater impact on reduction of stroke/SE was observed for warfarin TTR ≥55% or warfarin TTR <55% episodes compared to never on therapy (Figure 2). The outcomes from the lowest 25th warfarin TTR quartile (warfarin TTR <43.9%) were poor. This group reported the highest stroke/SE rates (5.37 per 100 PY) with the highest major bleed rates (17.32 per 100 PY), whereas stroke/SE rates from the highest 25th warfarin TTR quartile (warfarin TTR >71.3%) were only 0.93 per 100 PY with major bleed events of 4.59 per 100 PY (Figure 4).

Discussion

It is crucial for NVAF patients to continue antithrombotic therapy as well as maintain an adequate level of TTR for warfarin users to prevent strokes. This study shows that warfarin therapy with higher TTR range was associated with a reduction in stroke/SE for NVAF patients in a US managed-care setting. This finding is consistent with previous findings from other secondary analyses of clinical trial cohorts[12–16] and a retrospective observational study,[17] which emphasizes the importance of achieving and maintaining an adequate level of TTR. A significantly higher proportion of stroke/SE events occurred when the INRs were subtherapeutic (INR <2) as opposed to supratherapeutic (INR >3) (45.0% versus 13.8%, respectively). The absolute stroke/SE rates in the warfarin TTR ≥55% episodes were even lower than the event rates from the highest quartiles in some clinical trials;[12,13] therefore, more distinct differences between high versus low warfarin TTR were observed from our study. This may be due to treatment selection bias; physicians might prescribe warfarin for individuals with greater perceived benefits, or this could be explained by the continuous anticoagulation management efforts from pharmacist-led clinics in KPSC.

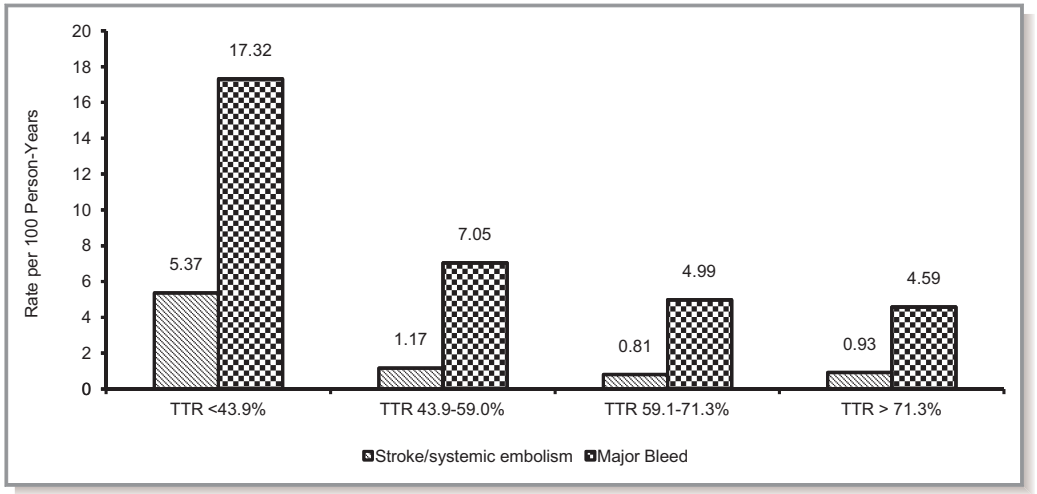

Figure 4. Stroke/systemic embolism and major bleed events by time in therapeutic range (TTR) quartiles.

These findings were consistent across $CHADS_2$ stratification; the stroke/SE rates remained very low even for higher-risk patients.

Our study found that bleeding rates in the higher-warfarin TTR episodes were comparable to the rates observed among aspirin therapy episodes; however, much greater bleeding rates were found in the low-warfarin TTR episodes. Some ad-hoc analyses reported similar findings,[13,14] and a systematic review article also found a negative correlation between warfarin TTR and hemorrhagic events.[28] However, it is not clear whether the higher bleeding events observed during the low-warfarin TTR episodes were associated with INRs that were supratherapeutic or subtherapeutic, as a similar proportion of bleeding events occurred when INRs were supratherapeutic and subtherapeutic (21.0% versus 24.8%, respectively). Other factors such as concomitant antiplatelet use, alcohol intake, comorbidities, or other patient behaviors may be associated with these findings. Our study showed much greater bleeding differences between high- versus low-warfarin TTR episodes compared to the results from clinical trials, which may have been due to the relatively tight control of INR in clinical trial settings.

Bleeding rates in the never on therapy episodes were higher than the warfarin TTR ≥55% episodes. This also may have been due to treatment selection bias. Older age, higher baseline bleed, and previous fall may explain part of these findings. Higher bleeding rates were observed after warfarin discontinuation. While this finding may seem counterintuitive, 92% of these patients in the study were defined as a warfarin discontinuation due to being discharged from the anticoagulation clinic. The potential reasons for discharge from the anticoagulation clinic are often associated with the high risk of bleeds, adverse side effects, patient refusal, and nonadherence. Future studies should consider investigating reasons for high bleeding rates in these groups to better understand the population.

This study revealed that 52.4% of NVAF patients with $CHADS_2$ ≥1 did not receive any antithrombotic therapy or were only on aspirin therapy. Interestingly, these percentages were consistent with higher $CHADS_2$ groups (52.6% for $CHADS_2$ ≥2, 55.3% for $CHADS_2$ ≥3), which has also been suggested by other observational studies.[6] However, an increasing trend of warfarin use was observed over the study period; 28.2% of the incident NVAF patients initiated warfarin during 2006–2008 and 36.0% in 2009–2011. This trend may be associated with the introduction of new guidelines calling for use of the $CHADS_2$ score to determine warfarin use.[29]

For warfarin users, 59.3% of person-time were either warfarin TTR <55% or off warfarin, which may represent care gaps. Moreover, this study also found a median TTR of 59% in the NVAF population. This TTR range was slightly higher than the mean TTR (53.7%) in office-based community practices in the United States,[30] and the differences may be larger given the fact that this study only included incident NVAF patients and TTR was calculated including the inception warfarin period. However, this study shows that a substantial portion of patients were not able to achieve a high TTR. Outcomes based on the TTR quartiles showed that the lowest quartile (TTR <44%) may have driven the worse outcomes observed in the low TTR episodes (ie, given that no linear relationship between TTR and outcomes was found: stroke/SE in the upper 2 TTR quartiles were similar: 4.59 per 100 PY for TTR >71.3% versus 4.99 per 100 PY for TTR 59.1% to 71.3%). While this information might be helpful for healthcare providers and policy-makers designing interventions to improve outcomes, it is important to note that this study does not provide solid evidence regarding an appropriate TTR threshold.

The primary strength of this study was the unique data source with the availability of EMR in a large cohort. Over 20 000 of the new NVAF patients' information were analyzed with maximum 6 years of follow-up considering longitudinal treatment patterns. In addition, we were able to separate aspirin use from the no-therapy group, and found notable differences in outcomes. Also, off-warfarin episodes were rigorously defined using actual anticoagulation pharmacist intervention data as well as lab and pharmacy records.

However, this study has limitations of observational research. This study depended on the availability and accuracy of the medical and pharmacy records provided. Accuracy or completeness of KPSC EMR data in terms of warfarin treatment has not been validated. Arbitrary grace periods (eg, 80 days for warfarin treatment and 180 days for aspirin treatment) to determine antithrombotic therapy episodes also have not been validated. Death information may not have been complete, since there is a delay in receiving death information from state and federal sources and then loading it into data systems. Challenges to defining hemorrhagic strokes and intracranial hemorrhages exist when using ICD-9-CM. ICD-9-CM code of 430, 431, and 432.x are interchangeably used to define hemorrhagic strokes and intracranial hemorrhages in retrospective observational studies.[31–33] There is likely to be a selection bias due to any lack of randomization. Patients with high risk of bleeding may be less likely to receive antithrombotic therapy, and treatment effect estimates are likely to be biased when these factors are unobserved and not controlled. Novel oral anticoagulation agents were not considered in this study due to a small sample size, which might influence treatment patterns. Generalizability of the study results may also be an issue since this study only evaluated patients in KPSC. Most of the warfarin patients in KPSC are managed by

anticoagulation clinics, which may lead to higher warfarin TTR or lower event rates compared to usual care. NVAF management and referral systems may be different outside the KPSC system.

Conclusions

To our knowledge, the association between real-world antithrombotic treatment patterns and clinical outcomes has not been widely studied. Episodes of warfarin TTR ≥55% were associated with a substantial reduction in stroke/SE events in patients with NVAF, while bleeding rates were similar to the rates of the aspirin use. In contrast, warfarin TTR <55% or aspirin-only therapy was associated with a moderate stroke/SE reduction, and warfarin TTR <55% episodes were also associated with a highly increased risk of bleed. Future studies should examine modifiable factors to improve outcomes for patients with suboptimal warfarin or for those who are off antithrombotic therapy.

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Stroke and Bleeding Risk Associated With Antithrombotic Therapy for Patients With Nonvalvular Atrial Fibrillation in Clinical Practice

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