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Antithrombotic Usage Patterns in the Era of New Oral Anticoagulant Options for Atrial Fibrillation

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ABSTRACT

Background: Appropriate treatment reduces the risk of stroke in patients with atrial fibrillation (AF). Despite the known benefits of warfarin, anticoagulation prescribing rates remain inadequate in high-risk patients. Over the last 6 years, 4 novel oral anticoagulants have been approved for use for stroke prophylaxis in non-valvular AF (NVAF), which may allow prescribers to tailor therapy for each NVAF patient.

Objective: The goal of this investigation was to determine the effect of dabigatran and rivaroxaban availability on the rate of anticoagulant prescribing at hospital discharge in patients with a principal diagnosis of NVAF.

Methods: A retrospective chart review of adult patients presenting with NVAF ($CHADS_2$ score ≥2) was conducted using a historical control group of patients from 2009 compared to patients admitted in 2012 following formulary availability of dabigatran and rivaroxaban. In addition to antithrombotic therapy prescribed, subsequent hospitalizations during a 1-year period were reviewed for major bleeding and stroke events.

Results: Two hundred patients were enrolled in the study. The rate of anticoagulant prescribing in the 2009 and 2012 groups was 68.3% and 77.1%, respectively ($p = .16$). Of the patients in the 2012 group prescribed an anticoagulant, 58 (64%) received warfarin, 26 (28%) received dabigatran, and 7 (8%) received rivaroxaban. One patient (1.2%) in the 2009 group and 4 patients (4.4%) in the 2012 group had a major bleed ($p = .4$).

Conclusion: There was no statistical difference in the rate of anticoagulant prescribing between the 2 groups. Despite the availability of additional anticoagulant options, the rate of prescribing remains suboptimal in this high-risk population.

Key Words— atrial fibrillation, dabigatran, rivaroxaban, stroke prophylaxis, warfarin

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Atrial fibrillation (AF) and flutter affect approximately 5 million people in the United States and are projected to affect up to 16 million people by 2050.[1] AF and atrial flutter can be attributed to valvular and non-valvular causes, although the major etiology is non-valvular (95%).[2] These conditions can be life-threatening due to a stroke rate that is 5 times higher than in the general population.[3] Additionally, estimated costs of stroke due to AF were $34 billion in 2008.[4] Anticoagulation with warfarin reduces the rate of cardioembolic events in these patients by approximately 64% (relative risk reduction) compared to no treatment.[3] Consequently, national guidelines for the management of AF including the American College

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of Cardiology (ACC)/American Heart Association (AHA) 2006 Guidelines and the American College of Chest Physicians (CHEST) 8th Edition of Antithrombotic Therapy Guidelines recommended that patients at high risk or with multiple risk factors for stroke (risk factors include prior stroke or transient ischemic attack, age ≥75, hypertension, heart failure, and diabetes) should receive long-term oral anticoagulation with warfarin therapy.[5,6] The guidelines recommend the use of a validated scoring system ($CHADS_2$) whereby all patients with a score of 2 or greater should be prescribed warfarin. In the updated AF section within the 2012 CHEST guidelines, the direct thrombin inhibitor dabigatran was added as an alternative to warfarin in this population.[7] In low-risk patients ($CHADS_2$ score of 1 or less), aspirin or no antithrombotic therapy may be utilized.

Despite the known benefits of warfarin, patients may not receive appropriate anticoagulation as indicated for stroke prevention. Multiple studies have documented the inadequate prescribing of anticoagulation in AF. Patients in the community setting have been documented to have the lowest rates of anticoagulation ranging from 11% to 32%, whereas those discharged from hospitals have rates of 38% to 44%.[8,9] Inadequate prescribing may be a result of the complexity involved in the pharmacodynamics and pharmacokinetics of achieving a therapeutic international normalized ratio (INR) with warfarin.[10] Indeed, a recent review of over 55,000 patients on warfarin for AF revealed that the overall time spent in the therapeutic range was 55% to 68%.[11] Therefore, alternative oral anticoagulants that are more easily managed by clinicians have been anticipated for decades.

Over the last 6 years, 4 direct acting oral anticoagulants, dabigatran (*Pradaxa*), rivaroxaban (*Xarelto*), apixaban (*Eliquis*), and edoxaban (*Savaysa*), have been approved by the US Food and Drug Administration (FDA) for stroke prophylaxis in non-valvular atrial fibrillation (NVAF). These agents do not require frequent laboratory monitoring and have a faster onset and offset of action and fewer drug interactions than warfarin.[12] Importantly, these newer agents have been compared to warfarin and were found to have similar or improved efficacy with lower rates of intracranial hemorrhage and similar or improved rates of major bleeding.[13-16] However, they are more expensive, have higher rates of major gastrointestinal bleeding (dabigatran, rivaroxaban, and edoxaban), and currently have no reversal agents for major bleeding.[17] With the exception of dabigatran, the efficacy of these newer agents is due to their reduction in hemorrhagic, not ischemic, strokes compared to warfarin. Theoretically, additional anticoagulant options should allow physicians to individualize therapy and thus increase prescribing rates in high-risk NVAF and non-valvular atrial flutter (NVAFL) patients. The purpose of this investigation was to determine the effect of the availability of dabigatran and rivaroxaban on the rate of appropriate anticoagulant prescribing upon hospital discharge in high-risk patients with a diagnosis of NVAF or NVAFL.

METHODS

This was a multicenter, retrospective chart review study utilizing electronic medical records from the years 2009 and 2012. Dabigatran and rivaroxaban were added to the hospital formulary by the Pharmacy & Therapeutics Committee in 2011 and 2012, respectively. The year 2009 served as a control group, where the only oral anticoagulant option was warfarin, whereas 2012 represented a year in which both dabigatran and rivaroxaban were available. During the time period of this study, inpatient warfarin therapy was primarily managed by a clinical pharmacy service and outpatient therapy was managed by physicians. The project design was approved by The University of Tennessee Institutional Review Board and was carried out at 4 adult urban hospitals in the Methodist Healthcare System, Memphis, Tennessee. Patients were identified through corporate patient financial services using the ICD-9-CM coding system for AF (427.31) and AFL (427.32), and every fourth patient was selected randomly for inclusion screening.

Although a power analysis was not performed, a total enrollment of 200 patients was planned, with equal distribution between the 2009 and 2012 groups. Patients were included if they were at least 18 years of age, were admitted to 1 of the 4 adult hospitals (Methodist University, Methodist North, Methodist South, or Methodist Germantown Hospitals), had NVAF or NVAFL, and had a $CHADS_2$ score of 2 or greater. Patients were excluded with a documented reason for no anticoagulation including recent bleeding event, fall risk, or advanced age in order to narrow the sample population to NVAF patients eligible for anticoagulation. The complete list of exclusion criteria is provided in **Table 1**.

Data collected during the index admission included sex, age, comorbidities to determine $CHADS_2$ score, antithrombotic therapy at discharge, renal function, and INR at discharge (warfarin group only). Each patient was observed for readmissions to any of the adult hospitals within the system for a

Table 1. Exclusion criteria

Other documented indication for anticoagulation[a]
Documented reason for no anticoagulation[b]
Acute CVA during index admission
Previous enrollment
AF/AFL post surgery
Discharged to hospice
Incomplete records

Note: AF= atrial fibrillation; AFL= atrial flutter; CVA = cerebrovascular accident.
[a] Cardioversion, ablation.
[b] Recent bleeding event, fall risk, advanced age.

period of 1 year after discharge from the index admission. Readmissions were reviewed for a diagnosis of stroke and major bleeding. Concomitant antiplatelet and anticoagulant medication use was captured for major bleeding events. In addition, hospital length of stay was collected for patients in the 2012 group.

Antithrombotic therapy was defined as aspirin, clopidogrel, warfarin, dabigatran, or rivaroxaban. Appropriate antithrombotic therapy was considered a prescription at discharge for any of the following anticoagulant agents: warfarin, dabigatran, or rivaroxaban. Stroke (ischemic or hemorrhagic) and NVAF or NVAFL were determined by physician diagnosis and documentation in the medical record. International Society on Thrombosis and Haemostasis criteria was utilized to determine major bleeding defined as (1) fatal bleeding and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, gastrointestinal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or (3) bleeding causing a fall in hemoglobin level of 2 g/dL or more, or leading to transfusion of 2 or more units of whole blood or red cells.[18]

The primary outcome of the study was to evaluate the use of appropriate antithrombotic therapy in 2012 compared to antithrombotic prescribing in 2009, prior to the availability of dabigatran and rivaroxaban. Secondary endpoints included incidence of stroke and major bleeding, and antithrombotic therapy prescribing by $CHADS_2$ score, age, sex, and co-morbidities were compared between groups. Additionally, length of stay during the index admission and the rate of readmission were evaluated for each oral anticoagulant in the 2012 group. Patients receiving dabigatran or rivaroxaban were evaluated for appropriate dosing based on package labeling.[19,20] IBM SPSS software (IBM, Inc., Armonk, NY) was used for statistical analysis. The 2-sample Student's *t* test was used to evaluate the statistical significance of differences in age and mean $CHADS_2$ score. The chi-square test was used to evaluate the statistical significance of differences in overall appropriate anticoagulation, appropriate anticoagulation by $CHADS_2$ score, and readmissions for stroke and bleeding events. A *p* value of less than .05 was considered statistically significant.

RESULTS AND DISCUSSION

A total of 513 patients were screened for enrollment. Of these, 200 met inclusion criteria and were enrolled (**Figure 1**). The majority of patients were excluded due to other indications for anticoagulation (61%). Twenty-four percent were excluded due to having a documented reason for no anticoagulation such as bleeding risk, fall risk, or increased age. Eighty-two patients were enrolled in the 2009 patient group and 118 in the 2012 patient group. Baseline characteristics were similar between the 2 groups (**Table 2**). The average $CHADS_2$ score was 2.4 ± 0.78 (95% confidence interval [CI], 2.3-2.6) and 2.6 ± 0.81 (95% CI, 2.4-2.7) for the 2009 and 2012 groups, respectively ($p = .33$).

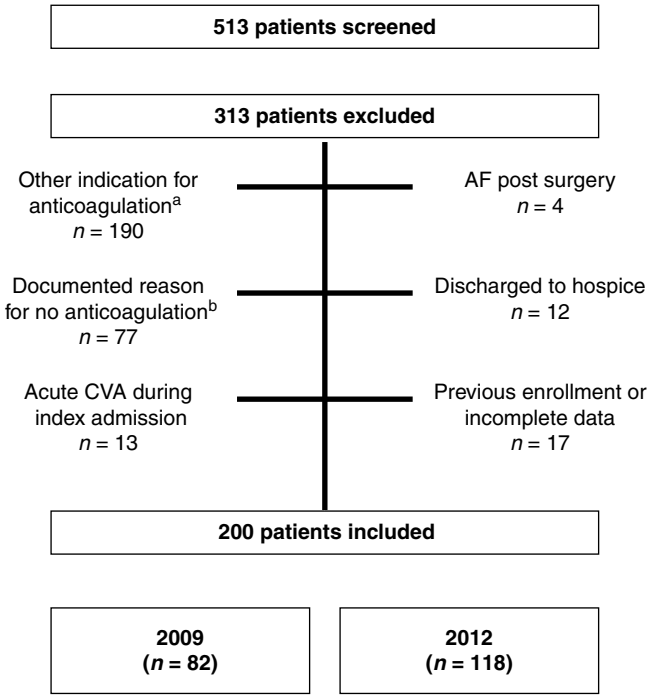

Figure 1. Patient screening process. AF = atrial fibrillation; CVA = cerebrovascular accident. [a]Cardioversion, ablation. [b]Recent bleeding event, fall risk, advanced age.

Table 2. Demographics

	2009 patient group (*n* = 82)	2012 patient group (*n* = 118)	*p* value
Age, mean years ± *SD*	68.3 ± 14.6	70.1 ± 12.6	.36
Female, *n* (%)	48 (58.5)	64 (54.2)	.55
$CHADS_2$ score, mean ± *SD*	2.4 ± 0.78	2.6 ± 0.81	.33
CHF, *n* (%)	35 (42.7)	52 (44.1)	.85
HTN, *n* (%)	75 (91.5)	111 (94.1)	.48
Age ≥75 years, *n* (%)	30 (36.5)	45 (38.1)	.824
DM, *n* (%)	43 (52.4)	58 (49.2)	.65
Prior stroke, *n* (%)	9 (11.0)	18 (15.3)	.38
Mean creatinine clearance, mean mL/min ± *SD*	60.6 ± 21.6	53.5 ± 20.2	.04

Note: CHF = congestive heart failure; DM = diabetes; HTN= hypertension.
[a] $CHADS_2$=stroke risk scoring system where 1 point is assigned to congestive heart failure, hypertension, age ≥75 years, and diabetes and 2 points for stroke/transient ischemic attack.

The primary outcome of prescribing rates of appropriate antithrombotic therapy occurred in 56 (68.3%) and 91 (77.1%) patients in the 2009 and 2012 groups (relative risk [RR], 1.1; 95% CI, 0.9-1.3; p = .16), respectively. Of those not receiving appropriate antithrombotic therapy, treatment included aspirin monotherapy, clopidogrel monotherapy, the combination of aspirin and clopidogrel, or no antithrombotic (**Table 3**). Only 9 patients received no antithrombotic therapy. When comparing inappropriate therapy by time periods, there was no statistical difference. Appropriate anticoagulant therapy based on $CHADS_2$ score (**Table 4**), sex, and comorbidities did not differ between groups. Examining prescribing patterns by patient age, it was found that more patients younger than 75 years received appropriate anticoagulation in 2012 compared to 2009 (RR, 1.3; 95% CI, 1.0-1.7; p = .02).

The secondary endpoints for the 2009 and 2012 groups were similar between the 2 groups: rate of ischemic stroke (1.8% vs 2.2%; p = .65; RR, 1.2; 95% CI, 0.1-13.3; p = .65), hemorrhagic stroke (1.2% vs 0%; RR, 0.2; 95% CI, 0.01-4.9; p = .23), major bleeds (1.2% vs 4.4%; RR, 2.5; 95% CI, 0.28-21.5; p = .4), and death (1.2% vs 0%; RR, 0.2; 95% CI, 0.01-4.9; p = .23). One (1.8%) patient in the 2009 group had a fatal major bleed on warfarin and expired (INR 4.4 at presentation). Four patients (4.4%) in 2012 had major bleeds on anticoagulation, including 3 gastrointestinal bleeds. Of the 4 major bleeds in 2012, 2 (2.2%) occurred with warfarin (INR 10 and 5.2 at presentation) and 1 (1.1%) each with rivaroxaban and dabigatran. Stroke occurred in 2 (1.8%) patients treated with warfarin (1 ischemic and 1 hemorrhagic) in the 2009 group and in 2 (2.2%) patients treated with warfarin in the 2012 group (both ischemic). No patients receiving dabigatran or rivaroxaban had a stroke. Additionally, 1 ischemic stroke occurred in a patient on aspirin monotherapy in 2012, and 1 major bleed in 2009 occurred in a patient receiving aspirin and clopidogrel.

Table 3. Inappropriate antithrombotic use

Stroke prophylaxis	2009 patient group (*n* = 26)	2012 patient group (*n* = 27)	*p* value
Aspirin	50% (*n* = 13)	40.7% (*n* = 11)	.49
Clopidogrel	7.7% (*n* = 2)	11.1% (*n* = 3)	1.0
Aspirin and clopidogrel	26.9% (*n* = 7)	29.6% (*n* = 8)	.83
No antithrombotic	15.4% (*n* = 4)	18.5% (*n* = 5)	1.0

Table 4. Appropriate anticoagulation prescribing by $CHADS_2$ score

$CHADS_2$ score	2009 patient group	2012 patient group	*p* value
2	65.5% (*n* = 38)	73.2% (*n* = 52)	.34
3	80% (*n* = 12)	85.2% (*n* = 29)	.64
4	75% (*n* = 4)	88.9% (*n* = 8)	.29
5	66.7% (*n* = 2)	66.7% (*n* = 2)	1.0
6	0% (*n* = 0)	0% (*n* = 0)	N/A

In the 2012 group, the majority of patients were treated with warfarin (63.7%), followed by dabigatran (28.6%) and rivaroxaban (7.7%). The mean length of hospitalization in the 2012 group by type of oral anticoagulation was 6.2 ± 3.6 days for warfarin, 5.8 ± 2.6 days for dabigatran, and 5.3 ± 1.9 days for rivaroxaban. The average INR at discharge for patients on warfarin was 1.7 ± 0.62 (95% CI, 1.6-1.9) and 1.8 ± 0.67 (95% CI, 1.6-2.0) in the 2009 and 2012 groups, respectively (p = .48). Appropriate dose adjustments for renal function were made in all patients on the direct acting agents except for 1 dabigatran patient.

DISCUSSION

To our knowledge, this is the first investigation comparing the appropriate anticoagulation prescribing rates for high-risk patients with NVAF following the availability of dabigatran and rivaroxaban. To date, several studies have demonstrated a shift in prescribing from warfarin to the new agents.[21-23] These results are consistent with our results, where the overall rate of anticoagulant prescribing did not increase with the availability of alternative agents. Therefore, the availability of dabigatran and rivaroxaban did not seem to impact the clinician's decision to prescribe oral anticoagulation in patients deemed to be candidates. For both time periods, the rate of appropriate anticoagulation was similar to rates reported in other studies (approximately 68%).[24] Approximately one quarter of patients did not receive appropriate anticoagulation when clearly indicated according to guidelines at the time of the study.[5,7]

We also found no difference in the secondary outcomes of major bleeding or stroke. The overall occurrence of stroke was very low, although there were no strokes in patients receiving dabigatran or rivaroxaban. Our data indicate that despite the known benefits of oral anticoagulation and new agents, barriers to prescribing remain.

In a study conducted by O'Brien et al, positive predictors of anticoagulation found to increase warfarin use included a history of stroke, heart failure, or male gender. Negative predictors of warfarin use included prior bleed, patient refusal, fall risk, and compliance.[25] None of the patients included in our study had documented negative predictors (ie, fall and bleeding risk, and increased age) of anticoagulation, as these patients were excluded. Given this exclusion, 100% of the patients in our study were candidates for appropriate anticoagulation, demonstrating that some other barriers to prescribing exist in our population.

Clinical trial data have demonstrated that dabigatran and rivaroxaban have more predictable pharmacokinetics, fewer drug interactions, and superior or comparable efficacy to warfarin. Alternatively, warfarin has known interpatient variability, and numerous drug, food, and disease interactions requiring frequent laboratory monitoring, which is highly dependent on patient compliance and can increase cost.[10,26-28] In reality, patient compliance may play a significant role in the frequency of laboratory follow-up, leading to an increase in health care costs. Therefore, the new agents are attractive alternatives to warfarin for some patients. In fact, a recent study demonstrated improved quality of life of patients on dabigatran compared to warfarin.[29] Furthermore, Choi et al evaluated dabigatran utilization and prescribing and reported patients had greater satisfaction with dabigatran compared to warfarin users.[30] However, some barriers may also exist with the direct acting agents, such as renal elimination, lack of a reversal agent, no readily available laboratory measurement, and cost.[4] Recently, a specific reversal agent for dabigatran has been approved, which may result in increased dabigatran use.[31] Some of these barriers likely were factors in our population, contributing to the overall suboptimal anticoagulation rate. The decision to prescribe

oral anticoagulation seems to remain based upon a myriad of physician and patient characteristics.

Despite recommendations for anticoagulation, 12% of the study population was treated with aspirin monotherapy. In 1991, the SPAF investigators published evidence demonstrating similar efficacy of aspirin to warfarin therapy, but noted that the warfarin arm of the study was underpowered to detect differences.[32] For some prescribers, aspirin is chosen due to a perceived reduced risk of bleeding. In 2007, Mant et al compared warfarin to aspirin and found warfarin to be at least as safe in patients 75 years old or older when examining the rate of extracranial bleeding.[33] When compared to the direct acting agents, the rate of major bleeding with aspirin is similar to another factor Xa inhibitor, apixaban (apixaban 1.4% vs aspirin 1.2%; hazard ratio, 1.13; 95% CI 0.74-1.75; $p = .57$).[34]

New guidelines from the AHA/ACC/HRS were recently published recommending the CHA_2DS_2-VASc scoring system to evaluate the risk of stroke for patients with AF.[3] These guidelines expand anticoagulation recommendations by assigning stroke risk to patients with vascular disease, ages 65 to 74 years, and female gender. With this expansion, the number of patients who are candidates for oral anticoagulation will increase, as the recommendation remains for a score of 2 or greater to be considered for anticoagulation. For patients to receive appropriate anticoagulation according to these updated guidelines, additional provider education seems warranted.

Unfortunately, evidence confirms the inadequate implementation of new guidelines, and previous educational efforts have produced varying and suboptimal results.[35,36] Pharmacists are uniquely positioned to improve outcomes in these patients through input in process improvement, formulary management, and policy development.[37] Although multidisciplinary educational initiatives should continue, an innovative and modern strategy utilizing computer technology may be more effective.[38,39] Computer algorithms to help prescribers identify patients with AF and specific stroke risk factors could form a clinical pathway for hospitalized patients. At our institution, a venous thrombosis prophylaxis (VTE) pathway alerts clinicians to patients needing VTE prophylaxis on the computer while entering orders. A similar clinical pathway for patients admitted with AF could be generated that would identify patients, calculate stroke risk score, and direct prescribers to acceptable options for anticoagulation.

Limitations

Limitations to our study include its retrospective design, small sample size, and limited control over confounding variables such as compliance or readmission to other hospitals. The small sample size and lack of power calculation likely contributed to the overall findings. We excluded patients with a documented reason for not using anticoagulation in an effort to obtain a population where all patients were considered candidates for therapy. Given that this exclusion relied on documentation, it is possible that patients with a perceived risk to anticoagulation were included in the analysis, reducing the overall percentage of appropriate anticoagulation found in our study. Finally, the risk of stroke was evaluated using the $CHADS_2$ score rather than the CHA_2DS_2-VASc score, because this was the scoring system in use when these patients were hospitalized.

Conclusions

In this study of hospitalized patients with a diagnosis of NVAF, we found no statistical change in the rate of anticoagulant prescribing with the availability of new agents. Ongoing evaluation of patients at risk is needed to increase the rate of appropriate anticoagulation. Ultimately, concordance with guidelines remains dependent upon prescriber education, pharmacovigilance, and the development of novel electronic clinical pathways.

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