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Using an Atrial Fibrillation Decision Support Tool (AFDST) for Thromboprophylaxis in Atrial Fibrillation: Impact of Gender and Age

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Abstract

Objectives—Among patients with atrial fibrillation (AF), female gender has been associated with an increased risk of stroke and a decreased likelihood of receiving oral anticoagulant therapy (OAT). The elderly are less likely to receive OAT due to concerns about falling and frailty. This study assessed the appropriateness of OAT among women and the elderly, looking for patterns of under-treatment or unnecessary treatment.

Design—Retrospective cohort study.

Setting—Primary care practices of an academic healthcare system.

Participants—1,585 adults with non-valvular AF seen between March 2013 and February 2014.

Intervention—Treatment recommendations were made by an Atrial Fibrillation Decision Support Tool (AFDST) based on projections for quality-adjusted life expectancy calculated by a decision analytic model that integrates patient-specific risk factors for stroke and hemorrhage.

Results—Treatment was discordant from AFDST-recommended treatment in 45% (326/725) of women and in 39% (338/860) of men ($p = 0.02$). While current treatment was discordant from recommended in 35% (89/258) of the elderly (age ≥ 85), and in 43% (575/1328) of patients < 85 years of age ($p = 0.01$) a large proportion of under-treated elderly patients were receiving aspirin as the sole antithrombotic agent.

Conclusion—Physicians should understand that female gender is a significant risk factor for AF-related stroke and incorporate this into decision-making about thromboprophylaxis. By

treating older patients with aspirin instead of oral anticoagulant therapy we are exposing them to a significant risk of bleeding with little to no benefit relative to reduction of AF-related stroke risk.

Keywords

atrial fibrillation; anticoagulation; gender differences; elderly; warfarin; novel oral anticoagulants; aspirin

INTRODUCTION

With the aging of the U.S. population, the number of individuals with atrial fibrillation (AF) will increase substantially from over 2.2 million to more than 3 million by the year 2020.¹ The contribution of AF to the burden of stroke also increases with age. In the Framingham study, 23.5% of strokes in individuals ≥ 80 years of age were due to AF.² It is also worth noting that due to the higher risk of AF-related stroke in the elderly, the impact of anticoagulation on the absolute risk reduction of stroke is greater in the elderly than in younger patients.

Surveys exploring barriers to optimal anticoagulation have identified numerous issues. Beyth and colleagues noted that physicians were less likely to prescribe warfarin for older patients.³ Others have shown that advanced age, female gender, and rural residency were associated with underuse of oral anticoagulant therapy.⁴ The therapeutic options for oral anticoagulant therapy (OAT) have evolved over time from vitamin K oral anticoagulants such as warfarin to a number of novel agents only recently approved for use in the United States by the FDA (dabigatran, rivaroxaban, apixaban, and edoxaban). The reasons for under-treatment of women are unclear, but likely relate to an incorrect perception that women are at lower risk of stroke.⁵ The pivotal physician-related factor seems to be an insufficiently balanced evaluation of the risk versus benefit of oral anticoagulant therapy. A recent systematic review comparing current treatment practices for stroke prevention in AF with a variety of published guidelines, including those of the American College of Chest Physicians (ACCP), and the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS), showed underuse of OAT in high risk patients in the majority of 54 studies reviewed.⁶ Among patients in 29 studies with a history of prior stroke or transient ischemic attack (TIA) who should all be receiving anticoagulant therapy, treatment levels averaged less than 60% (range 19% - 81.3%). Among high risk patients with a CHADS₂ score ≥ 2 treatment levels averaged less than 70% (range 39% - 92.3%). While there has been a trend towards improvement in utilization of anticoagulant therapy over the past decade, a recently published study of community-based practices in the Christiana Care Health System in northern Delaware continued to show substantial underutilization with almost one-third of high risk patients (CHADS₂ score ≥ 2) never receiving anticoagulant therapy despite the absence of identified barriers to such treatment.⁷ In an analysis of predictors of warfarin use among the 1,141 patients studied there was a trend for men to be more likely to receive treatment than women. In an analysis of predictors of warfarin interruptions, there was a trend towards an increased risk in women.

Middle-aged women have been found to be at significantly increased risk of death from AF.⁸ The addition of female gender to AF-related stroke risk scoring systems such as the CHA₂DS₂VASc underscores the observation that female gender is a risk modifier for AF-related stroke in the presence of additional stroke risk factors. That being said, the risk of stroke in women with AF is underappreciated by clinicians.⁹ Furthermore, studies have shown that populations of women at equivalent risk of stroke are less likely to receive anticoagulant therapy than men.¹⁰

There also is evidence that women, particularly older women, are less likely to receive OAT for AF.^{5, 11, 12} Fang and colleagues found that women not taking oral anticoagulants were at higher risk for stroke than men at both younger and older ages, with an adjusted relative risk of 1.6 (95% CI – 1.0 – 2.3) and 1.8 (95% CI – 1.4 – 2.3) respectively among patients 75 years of age and > 75 years of age.¹³

Others have found that older patients are less likely to receive anticoagulant therapy.¹⁴ Despite improvements over the past decade, still fewer than half of eligible elderly patients are receiving warfarin.^{15, 16} Surveys of physicians cite fall risk, dementia, and non-adherence as factors in elderly patients that deter them from prescribing warfarin in this population of patients.¹⁷⁻¹⁹

With the recent approval and availability of 4 non-vitamin K antagonist oral anticoagulants (NOACs), concerns have been raised regarding the safety of these agents in the elderly. Reasons for such concerns include the high frequency of renal impairment, low body mass index in the frail and most-elderly, and altered body composition of muscle and fat.²⁰ There have been a number of reports of increased bleeding risk among the elderly receiving treatment with dabigatran.^{21, 23} While no randomized trials have specifically examined the efficacy and safety of the NOACs in the elderly, a meta-analysis of 10 randomized trials (RCTs) of more than 25,000 patients 75 years, the risk of major bleeding was not significantly different between the NOACs and conventional therapy, usually warfarin. In the 4 trials involving patients with AF, NOACs were more effective than warfarin in the prevention of stroke in the elderly.²⁴

This study is aimed at producing a better understanding of the appropriateness of antithrombotic therapy* for thromboprophylaxis among women and the elderly, looking for patterns of either under-treatment or unnecessary treatment. It also provides some insight into the process of generating patient-specific reports regarding current and optimal anticoagulation therapy in an academic healthcare system. Our hypothesis was that in our cohort of AF patients we would find that women and older patients are under-treated with OAT compared with the most recent recommendations of the AHA/ACC/HRS.²⁵ We selected this guideline since it was both the most recent AF guideline released in the United States (March 2014), and it utilizes the more recently developed CHA₂DS₂VASc for determining AF-related stroke risk. We also hypothesized the same would be true even after accounting for AF-related stroke risk and bleeding risk on anticoagulant therapy, using an Atrial Fibrillation Decision Support Tool (AFDST) developed at our institution.

* Antithrombotic therapy – includes oral anticoagulants and antiplatelet drugs (aspirin, clopidogrel, prasugrel).

METHODS

We conducted a retrospective cohort study of 1,585 adults, ages 28-93, with non-valvular AF or flutter seen in ambulatory primary care practices of an academic healthcare system serving the Cincinnati tristate region. We used our health system's clinical data store to identify 9,270 patients with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis of atrial fibrillation (427.31) or atrial flutter (427.32) who did not have diagnoses of mitral valve disease (394.x), aortic valve disease (395.x), heart valve transplant (V42.2) or heart valve replacement (V42.3). We abstracted one year of data at the beginning of March 2014 (March 1, 2013-February 28, 2014). During this one-year period of time, 4,021 AF patients were seen in any of the outpatient practices in our health system, and 1,585 were seen in the primary care network (PCN). The institutional review board at the University of Cincinnati approved this study.

Information needed to calculate stroke risk using CHA₂DS₂VASc²⁶, major hemorrhage using HAS-BLED²⁷, and intracerebral hemorrhage (ICH)²⁷, was extracted from the clinical data store using the active problem list and a combination of laboratory values and clinical measurements. Current antithrombotic therapy was retrieved from the active medication list. Data were stored on a secure server at our Center for Health Informatics as discrete elements hosted on MYSQLTM. SAS data files were created as necessary for statistical analyses using unique coded patient identifiers. Further details are described separately.²⁸

Treatment recommendations were made by an Atrial Fibrillation Decision Support Tool (AFDST) which we developed. The computational engine of the AFDST is a patient-specific decision analytic model comprised of a 29-state Markov simulation which projects quality-adjusted life expectancy (QALE) for each of 3 strategies - 1) no antithrombotic therapy, 2) aspirin, and 3) oral anticoagulant therapy (warfarin in the base case) for each individual patient.²⁹ The decision model uses information from the EHR to integrate patient-specific risk factors for stroke and hemorrhage in its calculations.^{28, 29} Decision model construction and analysis was done using a standard computer program (Decision Maker, Boston, Massachusetts). Further details of the patient-specific decision analytic model are described separately.²⁸ While the decision analytic model used efficacy and bleeding risk data from warfarin for the oral anticoagulation strategy, the AFDST recommendation was for any oral anticoagulant if the warfarin strategy was better than either no antithrombotic therapy or aspirin. Thus, the AFDST was slightly conservative in its recommendations for OAT, given more recent data regarding the efficacy and bleeding risks associated with recently approved novel oral anticoagulants (NOACs). Finally, while recommendations of guidelines promulgated by the ACCP and the AHA/ACC/HRS are based solely upon stroke risk, the AFDST quantitatively incorporates both AF-related stroke and bleeding risk. SAS was used to perform simple descriptive statistical analyses and to develop multivariable regression models. All reported p-values are derived from models in which the provider is a random factor and denominator degrees of freedom are based on numbers of patients. The study alpha was a two-tailed $p = .05$, unadjusted for multiple tests.

RESULTS

Characteristics for the 1,585 patients in the study are described in Table 1. Patients' ages ranged between 28 years and 93 years, with a mean age of 70.5 years. Figure 1 shows the distribution of age across 5-year increments. Forty-six percent of patients were women. The mean CHA₂DS₂VASc and HAS-BLED scores were 3.7 and 2.1, respectively. Fifty percent of the cohort was receiving some form of OAT, most commonly warfarin (see Table 1). Only a small proportion of patients (11%) were receiving any of the non-vitamin K oral anticoagulants. There was a trend towards lower levels of OAT in women than in men but the difference was not statistically significant, 48% (347/726) and 52% (449/860) ($p = 0.06$), respectively.

The AFDST recommended OAT for 1,374 (87%) patients, aspirin for 65 (4%), and no antithrombotic therapy for 146 (9%) patients. Overall, antithrombotic therapy was concordant with AFDST recommendations in 58% of patients. Fifty-seven percent of patients for whom OAT or aspirin was recommended were receiving such treatment (788 and 37, respectively), while 64% of those for whom no antithrombotic therapy was recommended (94) were receiving no antithrombotic therapy. Antithrombotic therapy was discordant from that recommended by the AFDST in 42% of patients. Thirty-seven percent of patients for whom the tool recommended OAT were receiving only aspirin or no antithrombotic therapy; 2% of patients for whom the tool recommended aspirin were receiving either no antithrombotic therapy or OAT; and 3% of patients for whom the tool recommend no antithrombotic therapy were receiving either aspirin or OAT.

As shown at the bottom of Table 2a, current treatment was discordant from recommended treatment in 45% (326/725) of women and in 39% (338/860) of men ($p = 0.02$). In addition, 44% (321/725) of women were "under-treated," receiving aspirin or no OAT when OAT was recommended, while only 31% (263/860) of men were "under-treated" ($p < 0.0001$). Thus, women were 1.8 times more likely to be under-treated than men. The most recent update of the American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guideline for antithrombotic therapy in patients with AF recommends OAT for CHA₂DS₂VASc scores ≥ 2 , no antithrombotic therapy for a CHA₂DS₂VASc of 0, and states that any therapy is reasonable for a CHA₂DS₂VASc of 1²⁵. However, women with a CHA₂DS₂VASc of 1 (i.e., whose only risk factor is female gender) are at very low risk for stroke and no antithrombotic treatment is an appropriate choice, as recommended in European guidelines.³⁰ Comparing current treatment to the most recent AHA/ACC/HRS guideline-based therapy[†], 51% (370/725) of women and 37% (317/860) of men had treatment that was discordant with the guideline ($p < 0.0001$), resulting in an even greater disparity between the sexes (see Table 2b).

In non-stratified analyses, there was no significant difference in the use of OAT in older and younger patients; 55% (141/258) of patients 85 years of age or older were receiving OAT compared with 49% (654/1328) of those < 85 years of age ($p = 0.13$). As shown at the

[†]Although the AHA/ACC/HRS guideline makes no special mention of women with CHA₂DS₂VASc scores of 1, whose only risk factor is female gender, we have used the European Guideline recommendation suggesting no antithrombotic therapy for these patients due to very low stroke risk.

bottom of Table 3, among the very elderly (age ≥ 85) current treatment was discordant from recommended treatment in 35% (89/258), while treatment was discordant among 43% (575/1328) of patients < 85 years of age ($p < 0.01$). Similar proportions of patients under 85 years of age, 37% (497/1328) and ≥ 85 years of age, 34% (87/258) were “under-treated ($p = 0.30$). Aspirin use was no different between patients ≥ 85 and < 85 years of age (36%).

We further examined age categories in 5-year increments and found that discordant therapy was as high as 60-70% in those between the ages of 31 and 50 (see Figure 2).

Table 2a describes in what manner treatment was discordant among women and men compared with therapy recommended by the AFDST. Among 326 women with discordant treatment 99% (322/326) was due to under-treatment and 1% (4/326) was due to over-treatment (patients receiving either aspirin or OAT when no antithrombotic therapy was recommended, or OAT when only aspirin was recommended). Among 338 men with discordant treatment 81% (274/338) was due to under-treatment, while 19% (64/338) was due to over-treatment.

Table 3 describes in what manner treatment was discordant among patients < 85 and ≥ 85 years of age. Among 89 elderly patients with discordant treatment, 98% (87/89) of discordance was due to under-treatment and 2% (2/89) was due to over-treatment; whereas in those < 85 years of age, 88% (509/575) was due to under-treatment and 12% (66/575) was due to over-treatment.

We developed a multivariable logistic regression model to explore the impact of gender and age in order to investigate the hypothesis that female gender and advanced age were associated with an increased risk of discordant therapy. While the impact of female gender supported our initial hypothesis (Beta coefficient 0.36, $p = 0.0007$), we were surprised to find the opposite effect of increasing age (Beta coefficient -0.024 , $p < 0.0001$).

DISCUSSION

In our study of 1,585 adults, similar proportions of women and men were receiving OAT. However, when looking at discordance between actual treatment and recommendations of either an Atrial Fibrillation Decision Support Tool or the most recent AHA/ACC/HRS guideline, women with AF continue to receive less aggressive treatment to prevent stroke.

The sad irony is that female gender is associated with an increased risk of AF-related stroke. Thus, for any given set of risk factors, a woman has a higher risk of AF-related stroke than a man. While previously published studies have come to varying conclusions with regards to the presence or absence of gender differences in antithrombotic therapy for patients with AF^{4, 5, 11, 13, 31, 32, 33}, our study adds to the more contemporary evidence that gender differences in treatment are still occurring in some academic medical center settings, and we must remain vigilant in addressing them.

Numerous past studies have found advanced age to be a predictor of decreased use of oral anticoagulants.^{14, 31, 36} This is an issue since a growing proportion of patients with AF are elderly. It is estimated that by the year 2050, 50% of the roughly 5.6 million people with AF

will be over the age of 80 years.¹ Clearly, physicians have concerns about frailty and fall risk, cognitive deficits that might interfere with medication adherence, polypharmacy, and an increased risk of intracranial hemorrhage among others in the elderly. However, given the generally increased risk of AF-related stroke in older patients, the absolute gain in decreased stroke risk afforded by OAT may be greater in the elderly. In our cohort, we found no significant difference in the use of OAT in patients older or younger than 85 years of age. However, this does address whether such treatment is appropriate or not. When we looked at treatment compared with the recommendations of the AFDST, which takes both stroke and bleeding risk into account, we found similar proportions of patients older or younger than 85 years of age were under-treated. However, of some concern, a significant proportion of undertreated elderly patients were receiving aspirin as the sole antithrombotic agent. In interviews with physicians trying to understand why AFDST or guideline-appropriate therapy was not being given to these under-treated elderly patients, physicians cited concerns about bleeding risk. They felt that they “needed to do something” and that while aspirin is less effective than OAT, it has a lower associated bleeding risk. Recent data evaluating the efficacy of aspirin has shown a declining efficacy with increasing age, such that over the age of 77 years, aspirin has minimal if any impact on reducing AF-related stroke risk.³⁷ Furthermore, bleeding risk associated with aspirin is often underappreciated. The net result of treating elderly patients with aspirin is that we expose them to a significant risk of major hemorrhage while providing virtual no benefit in terms of stroke prevention. In 2007, the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA) of 973 patients aged 75 years or older, randomized to treatment with either warfarin or aspirin (75 mg), found the relative risk of stroke among patients receiving warfarin was 0.46 (95% CI, 0.26-0.79) compared with aspirin.³⁸ Furthermore, rates of major hemorrhage, including intracranial and extracranial bleeds, were not different between the warfarin- and aspirin-treated arms of the study. It has been proposed that the lack of difference in rates of major bleeding may have been due to selection bias in that over four-fifths of recruited patients were already taking either aspirin or warfarin. Thus, having already “survived” exposure to antithrombotic therapy, they may have been a population pre-selected to be at lower risk of major bleeding.³⁹ Nonetheless, anticoagulation of elderly patients with AF is beneficial unless there are compelling contraindications or the patient decides that the benefits are not worth the risk and hassle.

Four NOACs have been recently approved for use in the United States for AF.^{40,43} While they all possess somewhat different profiles, in general they are equally if not more effective than warfarin, and generally have a lower risk of major hemorrhage, in particular, intracerebral hemorrhage, and do not require routine monitoring.⁴⁴ Clinicians have questioned the generalizability of these results to a more elderly population. A recent meta-analysis evaluated evidence from 10 randomized controlled trials focusing on an elderly population of patients ≥ 75 years of age.²⁴ In the 4 trials of patients with AF, the NOACs were more effective than warfarin in preventing stroke in the elderly. In the full meta-analysis of all 10 studies, NOACs did not cause excess bleeding in the elderly. Similar results were noted in a summary of subgroup analyses of elderly patients in the phase 3 RCTs comparing warfarin with NOAC therapy.⁴⁵ Perhaps the NOACs can fill the niche now occupied inappropriately by aspirin therapy for elderly patients with AF.

Finally, contrary to our initial hypothesis, a larger proportion of patients under the age of 85 were receiving treatment that was discordant from the recommendation of the decision support tool. This was due largely to over-treatment of younger patients between the ages of 31 and 50.

CONCLUSIONS

We found that women in our cohort of AF patients receiving primary care in an integrated healthcare system of an academic medical center are regularly under-treated with antithrombotic therapy. Somewhat surprisingly, compared with older patients, a larger proportion of patients < 85 years of age are receiving treatment that is discordant from recommended therapy. Furthermore, in women and the elderly the major reason for discordant therapy is under-treatment; whereas in men and younger patients, a larger proportion of discordance is due to over-treatment.

What actions should these findings prompt? Physicians should understand that female gender is a significant and independent risk factor for AF-related stroke and factor this into their decision-making about thromboprophylaxis. While there are many reasons to be circumspect about treating older patients with OAT, we are under-treating these patients. Furthermore, in our efforts to avoid harm by treating older patients with aspirin instead of OAT we are actually exposing them to a significant risk of bleeding with little to no benefit relative to reduction of AF-related stroke risk. Finally, although they comprise a small proportion of patients with AF, we are over-treating young patients who are at minimal risk of AF-related stroke.

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Biography

Gregory Y.H. Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic and Sanofi Aventis.

Matthew L. Flaherty has served as a consultant to Boehringer Ingelheim, and has served on an advisory board for, as a consultant to, and on a speaker's program for CSL Behring.

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Cohort

Figure 1. Distribution of Patient Ages in Atrial Fibrillation Cohort

Five-year age categories are displayed on the x-axis, while the y-axis reports the proportion of patients in each age category in our atrial fibrillation cohort. The mean age is 70.5.

Figure 2. Proportion of Patients with Discordant Care by Age Category

Five-year age categories are displayed on the x-axis, while the y-axis reports the proportion of patients in each age category who had treatment that was discordant from the recommendations of the **A**trial **F**ibrillation **D**ecision **S**upport **T**ool (AFDST). Among patients between the ages of 31 and 50, the proportion with discordant care ranges between 50% and 70%.

Table 1

Patient Characteristics

Number	1,585
Age [mean, (SD)]	70.5 (13.4)
Female [n, (%)]	726 (46)
CHA ₂ DS ₂ VASc [mean, (SD)]	3.7 (1.9)
HAS-BLED [mean, (SD)]	2.1 (1.2)
Receiving oral anticoagulant therapy [n, (%)] [†]	797 (50)
Current treatment discordant from AFDST-recommended [‡] treatment (n, %)	664 (42)
Current Treatment	n, (%)
No antithrombotic therapy	214 (14)
Aspirin only	575 (36)
Warfarin	611 (39)
Aspirin/Clopidogrel	1
Aspirin/Prasugrel	1
Dabigatran	66 (4)
Rivaroxaban	83 (5)
Apixaban	27 (2)

[†]Warfarin, dabigatran, rivaroxaban, apixaban, edoxaban or aspirin/clopidogrel or prasugrel combination.

[‡]AFDST – Atrial Fibrillation Decision Support Tool.

Table 2a

Type of discordance among men and women with treatment discordant from AFDST[‡].

AFDST Recommended Treatment	Current Treatment	Women		Men	
		Number of Patients (n)	%	Number of Patients (n)	%
Oral Anticoagulant Therapy	None	78	24%	53	16%
	Aspirin	243	75%	210	62%
Aspirin	None	1	0%	11	3%
	Oral Anticoagulant Therapy	2	1%	14	4%
None	Aspirin	2	1%	24	7%
	Oral Anticoagulant Therapy	0	0%	26	8%
Total		326		338	

[‡]AFDST – Atrial Fibrillation Decision Support Tool.

Table 2b

Type of discordance among men and women with treatment discordant from guidelines.

Treatment Recommended by AHA/ACC/HRS Guideline	Current Treatment	Women		Men	
		Number of Patients (n)	%	Number of Patients (n)	%
Oral Anticoagulant Therapy [†]	None	83	22%	57	18%
	Aspirin	258	70%	231	73%
None [‡]	Aspirin	21	6%	22	7%
	Oral Anticoagulant Therapy	8	2%	7	2%
Total		370		317	

AHA/ACC/HRS indicates American Heart Association/American College of Cardiology/Heart Rhythm Society.

[†] Oral anticoagulant therapy recommended for CHA₂DS₂VASc score ≥ 2.

[‡] No antithrombotic therapy recommended for CHA₂DS₂VASc score = 0; or 1 in women without additional risk factors.

Table 3

Type of discordance among patients < 85 or ≥ 85 years of age with treatment discordant from AFDST[‡].

AFDST Recommended Treatment	Current Treatment	Age < 85		Age ≥ 85	
		Number of Patients (n)	%	Number of Patients (n)	%
Oral Anticoagulant Therapy	None	113	20%	18	20%
	Aspirin	384	67%	69	78%
Aspirin	None	12	2%	0	0%
	Oral Anticoagulant Therapy	16	3%	0	0%
None	Aspirin	25	4%	1	1%
	Oral Anticoagulant Therapy	25	4%	1	1%
Total		575		89	

[‡]AFDST – Atrial Fibrillation Decision Support Tool.