Anticoagulation for Patients with Atrial Fibrillation in Ambulatory Care Settings

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Background: **In the context of recently published guidelines, we studied anticoagulation for atrial fibrillation as part of stroke prevention.**

Methods: **The National Center for Health Statistics ambulatory care surveys use a multistage random sampling design consisting of 112 US geographic primary sampling units, nonfederal physician offices and hospital outpatient departments within those units, and patient visits to those offices and outpatient departments. Patient and visit characteristics were abstracted from 1771 medical records of patients with atrial fibrillation aged 20 years or older from 2001 to 2006, representing a national estimate of 6.1 million annual visits. The dependent variable was the prescription of warfarin. Independent variables included embolic risk factors, age, sex, race, payment source, region, urban-rural location, year, primary care provider status, number of visits during the past year, and documentation of aspirin. χ^2 and logistic regression measured associations with the prescription of warfarin. Analysis was performed in SUDAAN version 9.0 (RTI International, Research Triangle Park, NC).**

Results: **Among patients with atrial fibrillation, warfarin was prescribed during 52.2% of visits. Warfarin use was more likely in 2005 to 2006 than in 2001 and at visits covered by Medicare than by those covered by private insurance. Women and non-white patients were less likely to receive warfarin than their counterparts. Patients taking aspirin were less likely to get warfarin, but there were no significant differences because of age or the presence of risk factors. Warfarin use was more likely in the Northeast as compared with all other regions of the country.**

Conclusions: **Accepted guidelines for warfarin have been implemented during more than half of visits of patients with atrial fibrillation. Disparities exist among race, sex, and region. More attention is needed to appropriate prescribing of warfarin. (J Am Board Fam Med 2009;22:299–306.)**

Ischemic stroke is a persistent neurological deficit caused by occlusion of the supply of blood and thus oxygen to the brain, resulting in neuron loss. One risk factor for ischemic stroke is atrial fibrillation. This arrhythmia causes abnormal turbulence in atrial blood flow, promoting the formation of clots that can embolize to arteries in the brain and elsewhere. Because anticoagulation can reduce the incidence of ischemic stroke in patients with atrial fibrillation, this study examines anticoagulation as part of stroke prevention among patients with this arrhythmia. In 1999, the American Heart Association recommended warfarin for the prevention of recurrent strokes among patients with atrial fibrillation, or aspirin if warfarin was contraindicated.[1] In 2001, the American Heart Association recommended antithrombotic therapy (either warfarin or aspirin) for high-risk patients with atrial fibrillation who had not had strokes previously. This was based in part on a meta-analysis of 5 placebo-controlled trials that showed a 68% reduction in the relative risk of thromboembolic strokes in patients with atrial fibrillation who were taking warfarin. The predictors of high risk included age (older than 75 years, especially women); hypertension (especially a systolic blood pressure >160 mm Hg); diabetes mellitus, poor left ventricular function; rheumatic mitral valve disease; previous transient ischemic attack or stroke; and systemic embolism.[2] In 2002, the American Heart Association published updated clinical guidelines for primary prevention of stroke. Assessment of risk factors was recommended, start-

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ing at 20 years of age. Warfarin was again recommended for patients with chronic atrial fibrillation, with the alternative of aspirin (325 mg per day) for low-risk patients younger than 65 years of age.[3] In 2004, the American College of Chest Physicians published a set of antithrombotic therapy recommendations stratified by age and risk factors. For patients with atrial fibrillation and any risk factors, including age of ≥75 years, previous ischemic stroke, transient ischemic attack or systemic embolism, congestive heart failure, hypertension, diabetes mellitus, or mitral stenosis, anticoagulation with warfarin or another vitamin K antagonist was recommended. Either anticoagulation or aspirin (325 mg per day) was recommended for patients with atrial fibrillation between 65 and 75 years old without other risk factors. For patients younger than 65 without other risk factors, aspirin was recommended because the risks and burdens of anticoagulation therapy seemed to outweigh the gains in stroke prevention in that age group.[4]

After the 2001 clinical guidelines from the American Heart Association for stroke prevention, we investigated the prevalence of and factors associated with anticoagulation for patients with atrial fibrillation visiting US office-based physicians and hospital outpatient departments between 2001 and 2006. This study used data from a nationally representative sample of these visits.

Methods

The National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) use a multistage random sampling design. The stages include 112 US geographic primary sampling units; non-federal office-based physicians (NAMCS) and general hospital outpatient departments (NHAMCS) within those units; and patient visits to those providers. Both surveys are approved annually by the Ethics Review Board of the National Center for Health Statistics. The data set consisted of visit files collected from randomly assigned reporting periods from 2001 to 2006. Information about reasons for the visit, diagnoses, and medications were abstracted from a systematic sample of patient visits. Up to 3 reasons for visit were recorded and coded according to the National Center for Health Statistics Reason for Visit (RFV) Classification.[5] Up to 3 diagnoses were recorded for each visit and coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9).[6] Up to 6 (2001 to 2002) or 8 (2003 to 2006) medications could be recorded. Respondents were asked to record all medications that were ordered, supplied, administered, or continued during the visit, including prescription and over-the-counter drugs. For clarity, the term "use" is applied in this article to refer to any prescription or continuation of medications.

All records were included in the analysis from patients 20 years of age or older who had any listed diagnosis of atrial fibrillation (ICD-9 427.31) with no contraindications to treatment. Contraindications included malignant or benign brain neoplasms (ICD-9 191, 225); bleeding disorders (ICD-9 286 to 287); alcoholism (ICD-9 303); Alzheimer and other dementias (ICD-9 331); seizure disorders (ICD-9 345); chronic renal disease (ICD-9 403, 404, 582, 585 to 587, 593.9); cerebral hemorrhage (ICD-9 430 to 432); liver disease (ICD-9 570 to 573); peptic ulcer disease, gastritis, or duodenitis (ICD-9 531 to 535). Visits related to an injury, poisoning, or adverse effect of medical treatment, or for which the major reason for the visit was presurgical or postsurgical care (patient record form checkboxes), were excluded to eliminate trauma, anticoagulant toxicity, or recent surgery as contraindications to warfarin. A total of 1771 unweighted patient visits met these criteria, for a national estimate of approximately 6.1 million visits per year.

The dependent variable was the use of warfarin for patients with atrial fibrillation. Two other vitamin K antagonists were listed in the data set—dicumarol and anisindione—but preliminary analysis identified neither of them in the sample used for this study.

The independent variables included having any of the embolic risk factors listed in the 2001 American Heart Association recommendations, as well as age (younger than 65, 65 to 75, older than 75 years); race (white or other); primary payment source (private, Medicare, other); geographic region (Northeast, South, Midwest, West); metropolitan statistical area (urban, rural); survey year (2001 to 2006); whether the visit was to the patient's primary care provider; whether aspirin use was documented; and the number of visits during the last year (none or unknown, 1 to 2, 3 or more). It is reasonable to assume that patients with an

unknown number of prior visits lack continuity of care and are thus functionally equivalent to those known to have no prior visits; therefore, new patients were defined to include both of these groups.

Risk factors included stroke, diabetes, hypertension, congestive heart failure, rheumatic mitral valve disease, and arterial embolism, and were recorded as reasons for visit or diagnoses. Stroke was defined as cerebral or precerebral occlusion or stenosis, ischemic stroke, transient ischemic attack (ICD-9 433 to 437), or amaurosis fugax (ICD-9 362.34). Diabetes mellitus included ICD-9 250 or RFV 22050. Hypertension included ICD-9 401 to 405, or RFV 25050 or 25100. Congestive heart failure included ICD-9 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 and 428. Rheumatic mitral valve disease included ICD-9 394 and 396. Arterial embolism was coded as ICD-9 444.

Statistical Analysis

Sample weights were assigned based on the inverse probability of selection, with a non-response adjustment. The tables show the unweighted sample sizes, whereas the percentages represent weighted national estimates. χ^2 tests examined the bivariate associations between visit characteristics and the use of warfarin. Significance was set at $\alpha < .05$. Multivariate logistic regression models using odds ratios (ORs) with 95% CI were built to identify significant associations between visit characteristics and warfarin use after controlling for covariates. SUDAAN version 9.0 (RTI International) was used to account for the multistage sampling designs and weights.

Results

Among patients with atrial fibrillation and without contraindications, warfarin was prescribed or continued at 52.2% of visits. Sex, geographic region, the presence of embolic risk factors, and the number of visits within the last 12 months had significant bivariate associations with the use of warfarin (Table 1).

The multivariate model, adjusted for all of the independent variables, showed that sex and geographic region continued to be significant predictors of warfarin use. Survey year, primary payment source, race, and aspirin use emerged as additional significant predictors, but embolic risk factors and

Table 1. Percent of Outpatient Visits by Patients with Atrial Fibrillation during which Warfarin was Prescribed or Continued: United States, 2001 to 2006

Characteristics	N (%)	95% CI
All visits	1771 (52.2)	48.3–56.0
Risk factors*		
None	1059 (47.6)	42.4–52.9
Any	712 (58.5)	52.5–64.3
Age (years)		
<65	440 (49.8)	42.5–57.1
65–75	508 (49.6)	42.5–56.7
>75	823 (54.4)	49.1–59.6
Sex		
Female	873 (47.9)	42.8–53.1
Male	898 (56.4)	50.8–61.9
Race		
White	1563 (53.5)	49.4–57.5
Other	208 (40.5)	29.2–53.0
Primary payment source		
Private	392 (45.5)	38.5–52.6
Medicare	1094 (53.6)	48.5–58.5
Other	285 (57.1)	45.3–68.2
Region		
Northeast	497 (66.2)	59.5–72.3
Midwest	444 (55.2)	48.7–61.5
South	527 (41.1)	33.9–48.7
West	303 (49.9)	40.9–58.8
Metropolitan area		
Urban	1527 (52.6)	48.4–56.7
Rural	244 (50.4)	39.8–61.0
Survey year		
2001	282 (40.0)	30.4–50.3
2002	279 (51.8)	42.1–61.5
2003	272 (55.2)	43.5–66.3
2004	267 (50.7)	40.2–61.0
2005	270 (57.7)	46.6–68.1
2006	401 (56.6)	49.0–63.9
Primary care physician		
Yes	671 (52.5)	46.5–58.4
No	1100 (51.7)	46.7–56.8
Visits during last 12 months		
0 (including new patients)	208 (39.1)	27.0–52.7
1–2	421 (49.5)	42.7–56.2
≥3	1142 (54.6)	49.6–59.5
Aspirin		
Prescribed	281 (45.9)	36.4–55.6
Not prescribed	1490 (53.4)	49.2–57.5

*Risk factors: stroke, diabetes, hypertension, congestive heart failure, rheumatic mitral valve disease, arterial embolism.
N, unweighted sample size.

the number of visits became nonsignificant. Warfarin was more likely to be prescribed in 2005 (OR, 1.99; 95% CI, 1.10–3.61) and 2006 (OR, 2.02; 95% CI, 1.16–3.51) than in 2001. Warfarin was more likely to be prescribed during visits covered by Medicare (OR, 1.56; 95% CI, 1.01–2.39) than during those covered by private insurance. Non-white patients (OR, 0.49; 95% CI, 0.29–0.83) were less likely to be prescribed warfarin than white patients. Women (OR, 0.69; 95% CI, 0.50–0.94) were less likely to be prescribed warfarin than men. Warfarin was less likely to be prescribed at visits where aspirin was documented (OR, 0.62; 95% CI, 0.41–0.95). Warfarin was less likely to be prescribed in the South (OR, 0.35; 95% CI, 0.22–0.55); West (OR, 0.53; 95% CI, 0.33–0.87); and Midwest (OR, 0.60; 95% CI, 0.39–0.93) than in the Northeast (Table 2).

Table 2. Adjusted Odds Ratios for Prescribing or Continuing Warfarin during Visits by Patients with Atrial Fibrillation (N = 1771): United States, 2001 to 2006

Characteristics	OR (95% CI)
Risk factors*	
None	1.00
Any	1.40 (1.00–1.94)
Age (years)	
<65	1.08 (0.66–1.78)
65–75	0.90 (0.62–1.31)
>75	1.00
Sex	
Female	**0.69 (0.50–0.94)**
Male	1.00
Race	
White	1.00
Other	**0.49 (0.29–0.83)**
Primary payment source	
Private	1.00
Medicare	**1.56 (1.01–2.39)**
Other	1.82 (0.99–3.36)
Region	
Northeast	1.00
Midwest	**0.60 (0.39–0.93)**
South	**0.35 (0.22–0.55)**
West	**0.53 (0.33–0.87)**
Metropolitan area	
Urban	1.00
Rural	1.02 (0.61–1.70)
Survey year	
2001	1.00
2002	1.60 (0.92–2.78)
2003	1.73 (0.93–3.19)
2004	1.42 (0.77–2.62)
2005	**1.99 (1.10–3.61)**
2006	**2.02 (1.16–3.51)**
Primary care physician	
Yes	0.99 (0.68–1.43)
No	1.00
Visits during last 12 months	
0 (including new patients)	1.00
1–2	1.45 (0.68–3.09)
≥3	1.85 (0.96–3.56)
Aspirin	
Prescribed	**0.62 (0.41–0.95)**
Not prescribed	1.00

*Risk factors: stroke, diabetes, hypertension, congestive heart failure, rheumatic mitral valve disease, arterial embolism.
N, unweighted sample size; OR, odds ratio. Bolded values were statistically significant (confidence intervals did not include 1.00).

Discussion

A few studies have examined stroke prevention among patients with atrial fibrillation during the 1990s and early 2000s based on the available medical recommendations at that time. In a study using only the NAMCS data set of physician offices, anticoagulant use in patients with atrial fibrillation but without embolic risk factors increased from 13% in 1989 to 40% in 1993, but did not change thereafter through 1996.[7] In a second NAMCS-only study, approximately 47% of patients with atrial fibrillation at high risk for stroke were prescribed anticoagulants during 1999 to 2000.[8] In a study using the National Disease and Therapeutic Index data set, warfarin use in patients with atrial fibrillation increased to 51% in 2002.[9] However, little is known about the prevalence of anticoagulation for ischemic stroke prevention among patients with atrial fibrillation after 2002.

Our study used the most recently available nationally representative survey data about prescribing or continuing warfarin among outpatients with atrial fibrillation. To gain a more comprehensive picture of anticoagulation use, we added the NHAMCS sample of hospital outpatient departments to the NAMCS sample used in previous work. We found a significant increase in warfarin use for stroke prevention in 2005 and 2006 compared with 2001 after controlling for other variables. Future years' data may demonstrate further increases in the prescription of warfarin, especially

because warfarin use in patients with atrial fibrillation and a history of stroke was reaffirmed in 2004 by the American College of Chest Physicians[4] and in 2006 by the American Heart Association and American Stroke Association.[10]

Demographic Factors

A recent review showed that atrial fibrillation was associated with cardioembolic strokes among white patients.[11] In a study of nursing home residents with either atrial fibrillation or other anticoagulation indications, warfarin was prescribed less frequently for Asian, Pacific Islander, Hispanic, and non-Hispanic black patients than for non-Hispanic white patients.[12] Our results replicated the racial disparity in warfarin use with respect to the ambulatory care setting. More research is needed using either additional years of data or an oversampling of ethnic subgroups of interest to be able to make more detailed inferences for individual non-white subgroups.

We found that warfarin was less likely to be prescribed or continued for women than for men, although male sex is independently associated with severe bleeding with warfarin.[13] Women with symptomatic intracranial arterial stenosis are at significantly greater risk for ischemic stroke and vascular death.[14] Our results were consistent with a recent Irish national study suggesting missed opportunities to prevent stroke in women with atrial fibrillation aged 75 years or older.[15] Therefore, future studies are needed to understand better why older women with atrial fibrillation are less likely to be placed on warfarin than men.

We found that warfarin was less likely to be prescribed or continued in the South, West, and Midwest than in the Northeast. Other authors have found that southern patients were less likely than patients from all other regions to receive warfarin.[7] Our findings show a trend in the South to support that, although our confidence intervals for the South, West, and Midwest overlapped.

Embolic Risk Factors, Warfarin, and Aspirin

Aspirin is preferred over warfarin for patients with atrial fibrillation younger than 65 and without embolic risk factors. Therefore, we expected a lower prevalence of warfarin use among both younger patients and those at low risk. Although we did find a significantly lower bivariate prevalence of warfarin use in low-risk patients, this difference did not persist when adjusted for other factors in our model. We found no significant differences in warfarin use in either the bivariate or multivariate analysis among patients younger than 65, although Medicare coverage did emerge as a positive independent predictor of warfarin use in the multivariate model.

Because only slightly more than half of the patients were being prescribed warfarin regardless of risk, it is possible that the some of the remainder were on aspirin for anti-embolic prophylaxis. Indeed, our multivariate model demonstrated that documentation of aspirin was significantly associated with reduced odds of being prescribed warfarin. Despite this, we found that only approximately 53% of those not taking aspirin were on warfarin; among those who were taking aspirin, 46% were on warfarin as well.

A possible reason for using both warfarin and aspirin is that dual therapy is acceptable for additional protection against coronary artery disease.[8] However, the finding that only 58.5% of the patients with embolic risk factors are being prescribed warfarin is of some concern, in that clinical trials continue to show an increased benefit in stroke prevention versus possible adverse effects. In a study of British general practice patients with atrial fibrillation aged 75 or older and with or without comorbidities, one group was placed on warfarin to achieve an international normalized ratio of 2 to 3, and the other was given aspirin at 75 mg per day. Both groups were followed for up to approximately 5 years. The relative risk of ischemic stroke was 30% among patients on warfarin compared with those on aspirin, with no significant differences in the incidence of hemorrhagic stroke or other intracranial hemorrhage.[16]

Contraindications to Warfarin

One explanation for not prescribing warfarin when the patient seems to meet criteria for it is that there may be individual patient concerns about its use that are not captured in a cross-sectional survey. In a recent study of atrial fibrillation treatment at a large, urban medical center,[17] approximately 55% of patients received warfarin. Detailed review of the medical records revealed actual or perceived contraindications to warfarin in most of the remainder, leaving only approximately 7% without a documented reason for not prescribing warfarin. Approximately 40% of the patients had a history of

bleeding (either gastrointestinal or not) or coagulopathy. The other reasons for not prescribing warfarin included transient atrial fibrillation, risk of falling, and patient preference or compliance issues. Our study excluded patients with bleeding risks identified at the sampled visit, but patient history was not available in the 2001 to 2006 NHAMCS or NAMCS databases. Transient atrial fibrillation would be indistinguishable from chronic atrial fibrillation in our study, but the authors of the study cited above acknowledge that transient atrial fibrillation may not represent a true contraindication to anticoagulation. A standardized assessment of the risk of falling was not possible in our study, although we did exclude patients with alcoholism, dementia, and seizure disorders. Finally, although the NHAMCS and NAMCS capture the medications that were prescribed, they do not assess whether the patient actually took them. More research is needed to address historical contraindications and patient compliance to gain a full appreciation of the reasons for not using warfarin when it is otherwise indicated.

Patient and Physician Preferences

The prevalence of warfarin use is influenced by patient preferences, which could be modified by more intensive counseling on the objective benefits and risks of anticoagulation. It is critical to understand why physicians and patients accept the reduced efficacy of using aspirin alone in the face of high risk of stroke. Those patients at high risk for stroke receiving only aspirin may be afraid of bleeding that can be caused by warfarin. Or they may be put off by the inconvenience of having to monitor laboratory values, especially if they live in rural areas some distance from their source of care. In one study, the average patient with atrial fibrillation who had been on warfarin was willing to take it if it reduced the 2-year risk of stroke by approximately 2%. Even with an estimated 5% annual risk of stroke, only 1 out of 64 patients in that study would have opted against warfarin if they had had the information.[18] Another study examined how elderly patients were willing to accept the risk of either anticoagulation side effects or stroke after being informed of the objective published risks of anticoagulation. Only 61% of the total group wanted to be treated with warfarin, although the consensus criteria would have recommended that nearly all them should have been anticoagulated regardless of preference. But patient preference was not the only factor operating in that study; 45% of the patients who would have opted against anticoagulation were nonetheless receiving it, and 47% of those who would have opted for warfarin (whether recommended or not) were not receiving it.[19]

The complexity of establishing and monitoring anticoagulation is an issue for physicians as well as patients. In contrast to aspirin, warfarin therapy may involve frequent laboratory follow-up and the need to contact patients to adjust their doses to achieve anticoagulation parameters. Most importantly, a decision to anticoagulate a patient is not without risk. An adverse outcome is possible even when objective guidelines are followed. A recent survey of internists showed significant associations between their risk aversion styles and how frequently they would prescribe warfarin in various atrial fibrillation scenarios. Internists who would more regret not anticoagulating a patient who went on to have an ischemic stroke chose warfarin more frequently than those who would more regret anticoagulating a patient who then had a hemorrhagic stroke. Interestingly, the perceived risks of anticoagulation were 10 to 30 times higher than the actual risks documented in the literature. This perception was also associated with not prescribing warfarin. On the other hand, the perceived benefit of warfarin in stroke reduction was not associated with the frequency of prescribing it, despite perceived risks of ischemic stroke being approximately 3 times that reported in the literature.[20] Future research may show more congruence between recommendations and actual practice as the literature on risks and benefits of anticoagulation accumulates, especially to the extent that patient preferences are influenced by those of their physicians.

Limitations

Our definition for the patients at risk of having an ischemic stroke were based on a recorded reason for visit or diagnosis of hypertension (25.6% recorded), diabetes (6.4%), congestive heart failure (9.2%), or stroke (2.7%). Because there were only 3 fields each for reason for visit and diagnosis, some high-risk patients being seen for other conditions during that visit might have been missed. Alternatively, some patients might have been misclassified as low risk if they had one of these conditions but it was not recorded in one of the 3 fields. Similarly, our exclusion criteria may have missed some pa-

tients at risk for bleeding (2.5% recorded) if those diagnoses were not coded among the 3 possible ones during that visit or patients with contraindications related to trauma, surgery, or drug toxicity (5.5% recorded) if the reason for the sampled visit was not related to these. However, we felt that it was important to apply appropriate exclusion criteria within the constraints of the survey design.

It is possible that either warfarin or aspirin might have been missed on the patient record forms; only 6 to 8 medication fields were available. But because of the importance of anticoagulation in patients with atrial fibrillation, we believe that this is unlikely for warfarin in a sample selected for this condition. Under-documentation is more likely for patients taking aspirin for other reasons. However, we believe that if aspirin were being prescribed as an antithrombotic medication in lieu of warfarin, it would be less likely to go undocumented in a sample of patients with atrial fibrillation.

One limitation of a cross-sectional survey is that continuity of care over multiple visits cannot be examined directly. We did attempt to compensate for that by including variables on a primary care provider/patient relationship and the number of previous visits during that year. Although neither variable was associated with how often warfarin was prescribed or continued, it is possible that a longitudinal study design might uncover more patients who were on warfarin or documentation as to why other alternatives (including non-treatment) were chosen instead.

Conclusions

Warfarin is prescribed or continued during more than half of visits by patients for whom it is indicated for stroke prevention, but less so for women and for non-white patients than their counterparts. There are also independent effects of geographic region and primary payment source on warfarin use. Although some of the patients with embolic risk factors may be receiving aspirin as a reasonable alternative, this does not account fully for those not receiving warfarin. Improvement was found in prescribing warfarin during the latest 2 years of our study. Because anticoagulation guidelines have been updated and reaffirmed during the study period, continued monitoring of this critical preventive intervention is needed, along with research to determine mitigating factors and barriers to implementation.

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