Newly Detected Atrial Fibrillation and Compliance With Antithrombotic Guidelines

Nicole L. Glazer, MPH; Sascha Dublin, MD, PhD; Nicholas L. Smith, PhD, MPH; Benjamin French, MS; Lisa A. Jackson, MD, MPH; Jennifer B. Hrachovec, PharmD; David S. Siscovick, MD, MPH; Bruce M. Psaty, MD, PhD; Susan R. Heckbert, MD, PhD

Background: Guidelines recommend the use of antithrombotic therapy for stroke prevention in patients with atrial fibrillation (AF), but compliance with such guidelines has not been widely studied among patients with newly detected AF. Our objective was to assess compliance with antithrombotic guidelines and to identify patient characteristics associated with warfarin use.

Methods: A population-based study of newly detected AF (patient age, 30-84 years) was conducted within a large health plan. Cardiovascular disease risk factors, comorbid conditions, medication use, and international normalized ratios were abstracted from the medical record. Patients were stratified by embolic risk according to American College of Chest Physicians (ACCP) criteria. We analyzed the proportion of patients with AF receiving warfarin or aspirin (≥325 mg/d) during the 6 months following AF. Relative risk regression estimated the association of risk factors and patient characteristics with warfarin use.

Results: Overall, 73% of patients (418/572) with newly detected AF had evidence of antithrombotic use after AF onset. Among the 76% (437/572) of patients with AF at high risk for stroke, 59% (257/437) used warfarin, 28% (123/437) used aspirin, and 24% (104/437) used neither. The major predictor of warfarin use was AF classification; intermittent or sustained AF had relative risks for warfarin use of 2.8 (95% confidence interval, 2.2-3.6) and 2.9 (95% confidence interval, 2.2-3.7), respectively, compared with transitory AF.

Conclusions: Three quarters of the patients with newly detected AF received antithrombotic therapy, yet many at high risk of stroke did not receive warfarin. Atrial fibrillation classification, rather than stroke risk factors, was strongly associated with warfarin use.

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Author Affiliations: Cardiovascular Health Research Unit and Department of Epidemiology (Ms Glazer and Drs Smith, Siscovick, Psaty, and Heckbert), and Departments of Biostatistics (Mr French), Medicine (Drs Siscovick and Psaty), and Health Services (Dr Psaty), University of Washington, VA Puget Sound Health Care System (Dr Dublin), and Center for Health Studies, Group Health Cooperative (Drs Jackson, Hrachovec, and Heckbert), Seattle.

STROKE IS A DEVASTATING COMplication of atrial fibrillation (AF), occurring when blood clots formed in the atria embolize to the brain. Results of several randomized controlled trials have demonstrated that warfarin treatment significantly decreases the risk of stroke in patients with AF[1-9] and that the rate of stroke is modified by existing cardiovascular disease (CVD) risk factors.[4,10-13] The American College of Chest Physicians (ACCP) and the American College of Cardiology (ACC) recommend antithrombotic therapy for most patients with AF, with the selection of antithrombotic agent individualized to the patient's level of CVD risk.[14,15]

While there is some variation in guideline recommendations regarding antithrombotic therapy for AF, resulting from differences in risk stratification methods for ischemic stroke, both guidelines use age-based risk-stratification schemes. Aspirin (325 mg/d) or warfarin is recommended for stroke prevention, with the treatment choice dependent on the presence of additional stroke risk factors and contraindications to warfarin use. Risk stratification schemes are based on the results of clinical trials including patients with sustained AF or, less commonly, paroxysmal AF.[15] Guidelines recommend the selection of antithrombotic therapy based on the assessment of thromboembolic risk, irrespective of AF classification.

See also pages 229 and 239

Estimates of warfarin use among patients with AF range from 10% to 80%,[16-22] depending on the population studied. Studies of compliance with anticoagulation therapy guidelines among patients with AF have demonstrated underuse of therapy that could prevent the serious complication of ischemic stroke, particularly among elderly patients.[23,24] Compliance with evidence-based guidelines has not been widely studied among patients

with newly detected AF in the United States health care setting. Little is known regarding how AF duration and recurrence may affect the decision to administer antithrombotic therapy after AF onset. The objectives of this study were to assess the level of compliance with antithrombotic guidelines and to identify which risk factors and/or patient characteristics were associated with warfarin use.

METHODS

STUDY SETTING

The study setting was Group Health Cooperative (GHC), a large staff-model, nonprofit health maintenance organization headquartered in Seattle, Wash. Data for these analyses are from an ongoing, population-based, case-control study designed to identify novel risk factors for the development of AF and for major complications of AF. This article is a descriptive study of the prevalence and predictors of antithrombotic use among patients with AF only. The GHC clinical recommendations for AF anticoagulation therapy are based on the risk stratification guidelines set forth by the ACCP (**Table 1**).[15] This study was approved by the GHC human subjects review committee.

Table 1. American College of Chest Physicians Risk Stratification and Therapeutic Guidelines and Proportion of Newly Detected AF Cases at GHC in Each Risk Stratum

Risk Level	Patient Features	Therapeutic Guidelines	AF Cases, No. (%)
Low	Age <65 y and no other risk factors	Aspirin (325 mg/d)	87 (15)
Intermediate	Age 65-75 y and no other risk factors	Aspirin (325 mg/d) or warfarin (target INR, 2.5; range 2.0-3.0)	48 (8)
High	Any risk factor: prior ischemic stroke, TIA, or systemic embolism; age >75 y; moderate or severe LV systolic dysfunction and/or CHF; and history of hypertension or DM	Warfarin (target INR, 2.5; range, 2.0-3.0)	437 (76)

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; DM, diabetes mellitus; GHC, Group Health Cooperative; INR, international normalized ratio; LV, left ventricular; TIA, transient ischemic attack.

STUDY SUBJECTS

We defined newly detected AF cases as GHC members with a first clinically recognized lifetime episode of non–surgery-related AF. We identified all GHC enrollees aged between 30 and 84 years, who were assigned an *International Classification of Diseases, Ninth Revision* (*ICD-9*) code for AF (427.31 [atrial fibrillation] or 427.32 [atrial flutter]) during any inpatient or outpatient visit between October 1, 2001, and September 30, 2002, and who had never before been assigned an AF *ICD-9* code during their GHC enrollment. Abstractors reviewed medical records, covering a median of 20 years of enrollment prior to AF diagnosis, to verify the diagnosis and to confirm that the AF was of new onset; verified newly detected cases were retained as AF cases. There were 3 medical records abstractors, all trained by a single lead abstractor, who performed an extensive duplicate review of medical records. In a pilot study conducted at GHC before the present study was initiated, the sensitivity of an *ICD-9* code for AF was 95%, with 99% specificity.

We identified 1438 potential cases of newly detected AF during the study period. Subjects were excluded if (1) AF was determined not to be of new onset (n=333); (2) AF occurred during or after a surgical procedure and was resolved by hospital discharge (n=136); (3) subjects had fewer than 4 health care visits any time before the AF onset date (n=266); (4) subjects had a pacemaker implanted before AF onset, since the pacemaker could interfere with recognition of AF (n=66); and (5) hospitalized cases died during their hospitalization (n=41). After exclusions, there were 596 eligible cases of newly detected AF.

DATA COLLECTION

The GHC medical record includes notes from primary care and specialty physician visits, emergency department visit notes, discharge summaries, information from telephone contacts, problem lists, electrocardiograms, Holter monitor reports, and laboratory and diagnostic test reports. Abstractors reviewed the entire medical record to gather information on risk factors and comorbid conditions present prior to AF onset. Additional information was collected from the medical record regarding circumstances at AF onset, the persistence and/or recurrence of AF in the 6 months after diagnosis, and the results of electrocardiograms and echocardiograms performed during the interval from 3 months before to 6 months after diagnosis. Data on aspirin and warfarin use and measurements of the international normalized ratio (INR) during the 6-month follow-up period after AF onset were obtained from the medical record review.

We defined categories to describe the duration and persistence of AF (AF classification) using all evidence available in the medical record. The AF cases were classified into 3 mutually exclusive groups (transitory, persistent/intermittent, or sustained) based on the pattern of AF. Our classification scheme was designed to follow closely that of the ACC guidelines,[14] but some modification was required because not all AF cases were initially evaluated by cardiologists, and thus information on the effectiveness of cardioversion was not uniformly available. Transitory AF was defined as a single episode of AF lasting less than or equal to 7 days, without recurrence during the next 6 months. Atrial fibrillation was classified as persistent/intermittent if the initial AF episode lasted longer than 7 days or if AF recurred but sinus rhythm was also present during the 6 months (similar to the ACC/AHA/ESC category of persistent AF). We referred to this group as intermittent AF, since subjects with intermittent AF made up most of this group. Atrial fibrillation was classified as sustained if the patient was continuously experiencing AF during the 6 months after AF onset (similar to the ACC/AHA/ESC category of permanent AF). Subjects for whom AF class could not be determined were excluded (n=5), as were 19 subjects who were receiving warfarin at the time of AF onset.

Diabetes mellitus, hypertension, congestive heart failure, and stroke were defined as present at AF onset if there was a physician diagnosis in the medical record. Coronary artery disease was defined as history of myocardial infarction, coronary artery bypass graft, angioplasty, or definite or probable angina. During the 6-month follow-up period, compliance with ACCP recommendations specific to each risk level was defined as any use of aspirin at a dose of 325 mg/d or higher or warfarin (alone or combined) for the low- and intermediate-risk groups and any use of warfarin (alone or with aspirin) for the high-risk group.

Table 2. Characteristics of AF Cases, Overall and by AF Classification*

Characteristic	All AF Cases (n = 572)	AF Classification			*P* Value
		Transitory (n = 228)	Intermittent (n = 242)	Sustained (n = 102)	
Age, y	69.1 ± 10.9	67.2 ± 12.1	68.8 ± 10.1	74.0 ± 8.1	<.001
Female sex	264 (46.2)	116 (50.9)	113 (46.7)	35 (34.3)	.02
Married	371 (64.9)	146 (64.0)	163 (67.4)	62 (60.8)	.82
White	522 (91.3)	202 (88.6)	224 (92.6)	96 (94.1)	.40
Median GHC enrollment, y†	19.5 (10.7-29.3)	18.7 (9.4-28.8)	20.6 (11.5-29.2)	20.8 (11.7-30.4)	.29
Diagnosed hypertension	321 (56.1)	114 (50.0)	132 (54.6)	75 (73.5)	<.001
CAD‡	213 (37.2)	84 (36.8)	88 (36.4)	41 (40.2)	.79
Current angina	97 (17.0)	39 (17.1)	40 (16.5)	18 (17.7)	.97
History of MI	80 (14.0)	40 (17.5)	29 (12.0)	11 (10.8)	.13
History of ischemic stroke	45 (7.9)	12 (5.3)	22 (9.1)	11 (10.8)	.15
Chronic CHF	53 (9.3)	17 (7.5)	23 (9.5)	13 (12.8)	.31
History of claudication	33 (5.7)	14 (6.1)	12 (4.9)	7 (6.7)	.57
History of TIA	36 (6.3)	13 (5.7)	15 (6.2)	8 (7.8)	.76
Mitral valve disease	12 (2.1)	2 (0.9)	5 (2.1)	5 (4.9)	.06
Prosthetic heart valve	7 (1.2)	3 (1.3)	4 (1.7)	0	.44
Smoking, current	51 (8.9)	18 (7.9)	23 (9.5)	10 (9.8)	.78
BMI	30.4 ± 7.1	29.8 ± 6.7	30.6 ± 7.3	30.9 ± 7.4	.32
Diagnosed DM	113 (19.8)	38 (16.7)	48 (19.8)	27 (26.5)	.12
Most recent systolic BP, mm Hg	137 ± 20	138 ± 21	137 ± 19	136 ± 20	.93
Most recent diastolic BP, mm Hg	77 ± 12	77 ± 12	78 ± 11	77 ± 13	.64
ACCP risk category					
Low	87 (15)	45 (20)	41 (17)	1 (1)	<.001
Intermediate	48 (8)	25 (11)	19 (8)	4 (4)	
High	437 (76)	158 (69)	182 (75)	97 (95)	

Abbreviations: AF, atrial fibrillation; ACCP, American College of Chest Physicians; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; GHC, Group Health Cooperative; MI, myocardial infarction; TIA, transient ischemic attack.

*Data are given as number (percentage) or mean ± SD unless otherwise specified.

†For enrollment variable, value is given as median (25th percentile–75th percentile).

‡Defined as current angina, or history of myocardial infarction, coronary artery bypass graft, or angioplasty.

Possible contraindications to warfarin use were based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes (both primary and secondary) collected from all outpatient and inpatient visits during the year before AF onset.[19] Binary variables were created representing the presence or absence of the following contraindications: alcohol or other drug abuse/dependence, prior intracranial, gastrointestinal or other hemorrhage, prior cerebral aneurysm, predisposition to falls, cirrhosis or hepatitis, renal insufficiency, hemorrhagic tendencies or other blood dyscrasias, and perceived barriers to compliance (the *ICD-9* codes used to define warfarin contraindication variables are available at http://depts.washington.edu/gim/research/research_chru_appendix.htm).

DATA ANALYSIS

We estimated the proportion of AF cases receiving warfarin or aspirin (≥325 mg/d) during the 6-month follow-up period, and the proportion of time the warfarin users' INRs were within the recommended target range (2.0-3.0). To assess the proportion of time INRs were within the target range, INRs for each day of follow-up were estimated using linear interpolation between existing values among subjects with 2 or more INR measures.[25] We allowed warfarin therapy to be discontinued and then reinstituted but assumed that therapy was discontinued if not given for 30 consecutive days. Since data on medication use and INR results were not available from inpatient hospitalizations, we did not count hospitalized person-time during follow-up.

We examined a priori identified clinical risk factors, patient characteristics, and possible warfarin contraindications for their association with warfarin use. Each of the variables was examined in a separate model and adjusted for sex, age as a categorical variable, and AF classification. Relative risk (RR) and 95% confidence intervals (CIs) were directly estimated using RR regression.[26] A generalized linear model was fit using a log-link function and a Poisson distribution, with robust Huber/White/sandwich variance estimates. Statistical analyses were performed using Stata 8.0 software (StataCorp, College Station, Tex).

RESULTS

After exclusions, there were 572 eligible cases of newly detected AF. Among these patients, the mean age was 69 years, 46% were female, and 91% were white (**Table 2**). Approximately three quarters of the patients with AF had at least 1 additional risk factor for stroke (eg, aged >75 years or history of congestive heart failure, hypertension, stroke, transient ischemic attack, or diabetes mellitus). Age and sex varied significantly among AF classifications, as did ACCP risk categories and the proportion of those with hypertension.

Among all AF cases, 76% were in the highest ACCP stroke risk category, 8% in the intermediate category, and 15% in the low-risk category (Table 1). Overall, 60% of patients were compliant with the ACCP recommenda-

tions specific to their risk level. Of the patients with AF, 73% had evidence of antithrombotic treatment in the 6-month period after initial diagnosis (**Figure 1**). Among those in the high-risk group, 48% used warfarin alone, 11% used both warfarin and aspirin, and 24% received no antithrombotic therapy. Warfarin use differed significantly across risk strata ($P=.004$). We examined antithrombotic use limited to the first 30 days following AF onset and found no difference when compared with antithrombotic use during 6-month follow-up, indicating that few persons initiated therapy between 1 and 6 months after onset.

Overall, 25% of transitory, 74% of intermittent, and 77% of sustained AF cases were treated with warfarin (**Figure 2**). The proportion of cases left untreated was highest among transitory cases (44%) and considerably lower among intermittent (16%) and sustained cases (13%). Both warfarin and aspirin use differed significantly across AF classification ($P<.001$ and $P=.007$, respectively). Patterns of antithrombotic use across AF class were similar when examined in subgroups by ACCP stroke risk (**Figure 3**).

We examined the proportion of person-time spent below (<2.0), within (2.0-3.0), or above (>3.0) the recommended therapeutic range of INR. Of 315 patients who received warfarin during follow-up, 296 had at least 2 available INR measurements. On average, the target INR range was maintained 48% of the time, below target range 33% of the time, and above target 19% of the time. After excluding the first 60 days of INR results, the distribution did not substantially change. Time within the target range did not differ by AF classification ($P=.13$) or stroke risk ($P=.54$).

Overall, 32% of AF cases had a possible contraindication to warfarin use; 28% of warfarin users compared with 37% of nonusers had a warfarin contraindication ($P=.02$). Exclusion of subjects with a possible contraindication to warfarin (n=181) did not substantially change the distribution of warfarin or aspirin use across AF classes or ACCP risk groups.

Atrial fibrillation classification was the strongest predictor of warfarin use (compared with transitory AF, the RR for intermittent AF was 2.8 [95% CI, 2.2-3.6] and the RR for sustained AF was 2.9 [95% CI, 2.2-3.7]), whereas none of the stroke risk factors or warfarin contraindications were significantly associated with warfarin use after adjustment for age, sex, and AF classification (**Table 3**). When comparing the sustained AF group directly with the intermittent group, there was no difference between the 2 in terms of association with warfarin use (compared with intermittent AF, the RR for sustained AF was 1.0 [95% CI, 0.9-1.2]). Further adjustment for ACCP risk stratum or for individual risk factors including diabetes melitis, prior coronary artery disease, or hypertension did not substantially change any of the RR estimates in Table 3.

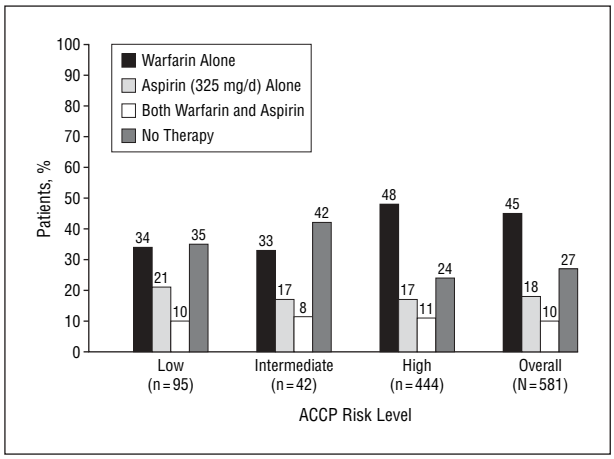

Figure 1. Use of antithrombotic therapy, overall and by American College of Chest Physicians (ACCP) stroke risk.

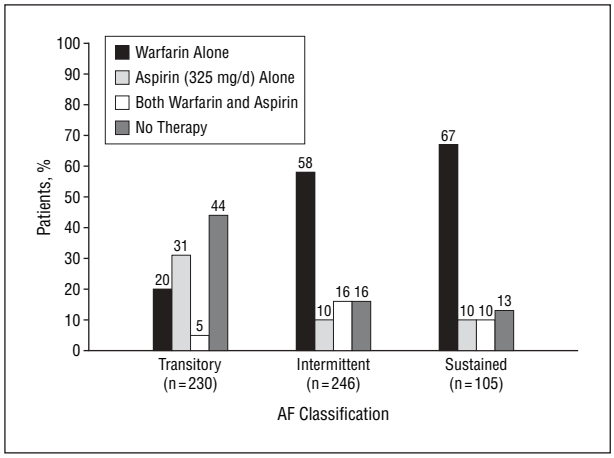

Figure 2. Use of antithrombotic therapy by atrial fibrillation (AF) classification.

COMMENT

In this population-based study, approximately three quarters of patients with newly detected AF received antithrombotic therapy (warfarin or aspirin) during the first 6 months of follow-up. However, 41% of patients at high risk of stroke did not receive warfarin despite guidelines recommending anticoagulation for such subjects. Warfarin use varied significantly among ACCP risk strata, while aspirin use was similar across strata. Anticoagulation varied among AF classes, with intermittent and sustained groups having significantly higher rates of warfarin use compared with patients with transitory AF. Individual stroke risk factors were not predictors of warfarin use. Rather, AF classification was the strongest predictor of use, and this association persisted even after adjustment for stroke risk factors.

Reports of warfarin use in newly detected AF have ranged from 17% to 65%, depending on the study population and pattern of AF.[20-22] The rates of warfarin use in our study are consistent with a study of new-onset AF in Canada and the United States, which found that 65% of patients were prescribed warfarin after diagnosis.[20] However, rates of warfarin use in our study were much higher than those reported in the United Kingdom, which found that 17% of patients with new-onset paroxysmal and 26% of patients with chronic AF received warfarin within 3 months following diagnosis[21,22] compared with

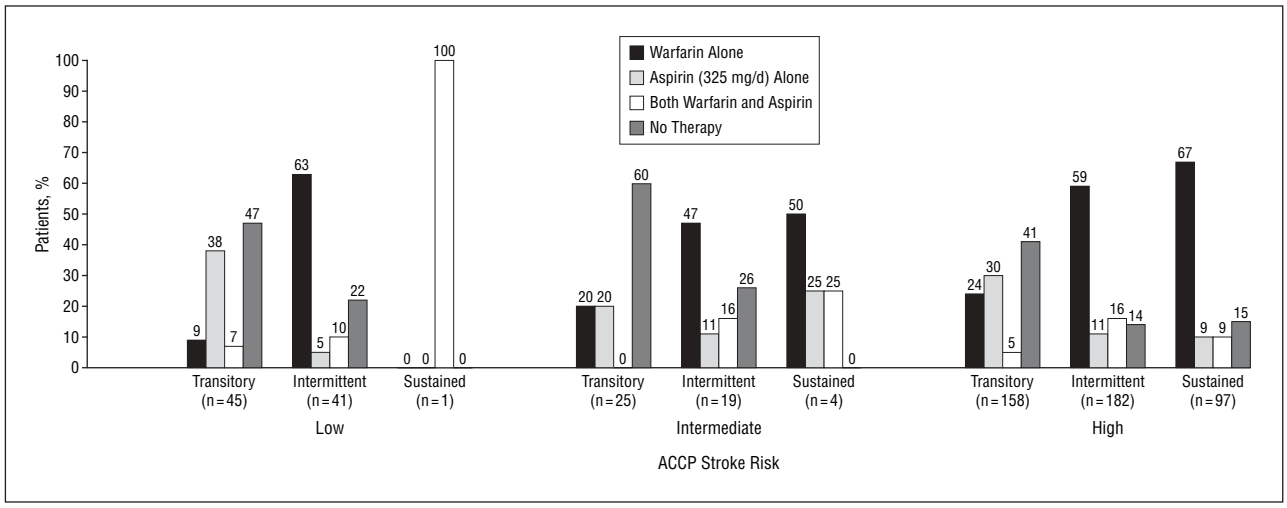

Figure 3. Use of antithrombotic therapy by atrial fibrillation classification and American College of Chest Physicians (ACCP) stroke risk.

Table 3. Predictors of Warfarin Use Among 572 GHC Patients With Newly Detected AF

Variable	Relative Risk (95% CI)*
Age, y	
50-75	1.0
<50	0.5 (0.2-1.1)
>75	0.9 (0.8-1.1)
Male sex	1.1 (1.0-1.3)
AF classification	
Transitory	1.0
Intermittent	2.8 (2.2-3.6)
Sustained	2.9 (2.2-3.7)
Married	1.2 (1.0-1.4)
CAD†	1.0 (0.9-1.1)
Ischemic stroke or TIA	1.0 (0.8-1.2)
CHF/LV dysfunction	1.1 (1.0-1.3)
Diagnosed hypertension	1.0 (0.8-1.1)
Diagnosed diabetes mellitus	1.1 (1.0-1.3)
Any contraindication	0.8 (0.7-1.0)
Renal insufficiency	0.7 (0.5-1.1)
Prior hemorrhage	0.8 (0.6-1.1)
Predisposition to falls	0.9 (0.7-1.1)
Barriers to compliance	1.0 (0.7-1.3)
Alcohol or drug abuse	0.7 (0.3-1.4)

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; GHC, Group Health Cooperative; LV, left ventricular; TIA, transient ischemic attack.

*All models were adjusted for sex, age modeled as a categorical variable (<50, 50-75, and >75 years), and AF classification.

†Defined as current angina or history of myocardial infarction, coronary artery bypass graft, or angioplasty.

25% of transitory and 75% of patients with intermittent and sustained AF, respectively, in our study. Only 15% of patients with intermittent or sustained AF in our study were untreated, whereas close to 40% of patients with chronic AF in the United Kingdom study did not receive warfarin or aspirin.[22]

Previous investigations of predictors of warfarin use have found conflicting results. In studies of prevalent AF, hypertension,[27] congestive heart failure,[17,27] cerebrovascular disease,[17,27] and male sex[28] have been reported as predictive of warfarin use, while older age[17,28,29] and prior hemorrhage[17,27] have been found to be deterrents to anticoagulation. In studies of new-onset AF, moderate associations with warfarin use have been found for some stroke risk factors such as hypertension and congestive heart failure, while associations with other risk factors such as prior cerebrovascular disease and diabetes mellitus have been conflicting.[19,20,22] Older age and contraindications to warfarin have been found to be a deterrent to anticoagulation among populations with new-onset AF.[19,20,22] In our study, individual risk factors for stroke were not predictive of warfarin use, nor did we find a negative association with increasing age, female sex, or warfarin contraindications. This is consistent with previous observations that the association of stroke risk factors with warfarin use in new-onset AF appears to be smaller than expected.[19,20,22]

Over three quarters of patients with newly detected AF in our study were classified as being at high risk for stroke. This is likely owing to the underlying demographics of GHC patients with AF, since 70% of the patients in our study were older than 75 years or were hypertensive. The ACCP antithrombotic therapy recommendations are based on stroke risk, regardless of the pattern of AF presentation. Yet, our study indicates that in this population, AF classification, rather than stroke risk factors, was strongly associated with warfarin use. This is consistent with the study by Reynolds et al,[20] who found that AF recurrence was stronger than any individual stroke risk factor in predicting warfarin use. The results of our study indicate that physicians (and patients) may be disinclined to initiate warfarin therapy if the patient presents with a single episode of AF without recurrence, despite the patient's underlying risk of stroke. This may be because the AF was resolved by the time a treatment decision was made.

Several limitations should be acknowledged. Compared with the United States, the GHC population has fewer blacks and higher education and income distributions.[30] The results of this study may not be generalizable to other less affluent populations or to those without consistent access to health care. In addition, we were

unable to determine to what extent noncompliance with treatment guidelines may be due to physician noncompliance as opposed to patient refusal of treatment.

Since we were only able to include clinically recognized AF, it is possible that some cases of AF may have been present prior to clinical recognition and were not truly "new onset." There may have been additional asymptomatic or transitory cases that were not identified. Misclassification of AF class was possible, although we attempted to minimize this bias through detailed review of physician assessments and diagnostic tests.

Data on time spent within given INR ranges was limited by the fact that 39% of warfarin users had only 2INRresultsavailableduringfollow-up.Warfarincontraindication data came from *ICD-9* codes during the year before AF onset, rather than medical record review, and misclassification or incomplete ascertainment of contraindications is possible.[31] It is possible that contraindications present prior to 1 year before the AF diagnosis could have affected treatment decisions. This potential misclassification may account for the null association between contraindications and warfarin use.

The strengths of this study include its population-based design and inclusion of only newly detected AF cases. All subjects were enrollees of a health maintenance organization and had similar access to health care. Data on covariates other than warfarin contraindications came from detailed review of medical records, which are more sensitive than administrative data for capturing this data. We also had information on duration and persistence of AF, allowing examination of treatment patterns by AF classification.

The lack of influence of stroke risk factors on warfarin use in patients with AF is concerning, given that several randomized controlled trials demonstrate that the rate of stroke in patients with AF is related to coexistent CVD risk and that warfarin treatment effectively reduces this risk.[1-9] The role of anticoagulant therapy has not been completely evaluated in patients with paroxysmal AF, although results from clinical trials suggest that stroke risk is similar for paroxysmal AF as with persistent or permanent AF.[4,32,33]

The low anticoagulation rate of patients with transitory AF in our study is particularly significant, considering that 69% of the transitory group was classified as being at high risk for stroke. Future studies are necessary to evaluate the burden of stroke among patients with transitory AF and to estimate the proportion of stroke that may be due to noncompliance with treatment guidelines among such patients. Further studies evaluating whether patients with transitory AF truly have stroke risk comparable to patients with persistent or permanent AF are warranted and will help physicians determine the best course of treatment for patients with AF.

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Correspondence: Nicole L. Glazer, MPH, University of Washington Cardiovascular Health Research Unit, 1730 Minor Ave, Suite 1360, Seattle, WA 98101 (nlg@u.washington.edu).

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Additional Information: The *ICD-9* codes used to define warfarin contraindication variables are available at http://depts.washington.edu/gim/research/research_chru_appendix.htm.

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