Electrophysiology

Stroke With Intermittent Atrial Fibrillation: Incidence and Predictors During Aspirin Therapy

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OBJECTIVE	This study was performed to characterize the risk of stroke in elderly patients with recurrent intermittent atrial fibrillation (AF).
BACKGROUND	Although intermittent AF is common, relatively little is known about the attendant risk of stroke.
METHODS	A longitudinal cohort study was performed comparing 460 participants with intermittent AF with 1,552 with sustained AF treated with aspirin in the Stroke Prevention in Atrial Fibrillation studies and followed for a mean of two years. Independent risk factors for ischemic stroke were identified by multivariate analysis.
RESULTS	Patients with intermittent AF were, on average, younger (66 vs. 70 years, $p < 0.001$), were more often women (37% vs. 26% $p < 0.001$) and less often had heart failure (11% vs. 21%, $p < 0.001$) than those with sustained AF. The annualized rate of ischemic stroke was similar for those with intermittent (3.2%) and sustained AF (3.3%). In patients with intermittent AF, independent predictors of ischemic stroke were advancing age (relative risk [RR] = 2.1 per decade, $p < 0.001$), hypertension (RR = 3.4, $p = 0.003$) and prior stroke (RR = 4.1, $p = 0.01$). Of those with intermittent AF predicted to be high risk (24%), the observed stroke rate was 7.8% per year (95% confidence interval 4.5 to 14).
CONCLUSIONS	In this large cohort of AF patients given aspirin, those with intermittent AF had stroke rates similar to patients with sustained AF and similar stroke risk factors. Many elderly patients with recurrent intermittent AF have substantial rates of stroke and likely benefit from anticoagulation. High-risk patients with intermittent AF can be identified using the same clinical criteria that apply to patients with sustained AF. (J Am Coll Cardiol 2000;35:183–7) © 1999 by the American College of Cardiology

In about 25% of elderly people who have atrial fibrillation (AF), the dysrhythmia is intermittent, spontaneously arising and remitting with highly variable frequency, duration and symptoms (1–6). Stroke rates and risk factors are less well characterized in patients with intermittent (paroxysmal) AF as compared with those with sustained (constant) AF (7–9). Patients with intermittent AF are typically younger and have less associated cardiovascular disease versus those with sustained AF. While it is commonly held that patients with intermittent AF have a lower risk of stroke than those with sustained AF (1,10,11), the pattern of AF has not emerged

as an independent predictor of stroke in multivariate analyses of elderly cohorts with this dysrhythmia (12–17). Regarding selection of antithrombotic prophylaxis, it is not known whether risk factors used to stratify stroke risk in AF patients apply specifically to those with intermittent AF.

We analyzed stroke rates and predictors of stroke among 460 participants with intermittent AF given aspirin in the Stroke Prevention in Atrial Fibrillation (SPAF) I-III studies and compared them with participants with sustained AF.

METHODS

Participants in the SPAF I, II and III clinical trials (1987 to 1997) assigned to aspirin (325 mg/day) or to a combination of aspirin plus inefficacious fixed-dose warfarin in the SPAF III trial were considered in this analysis. The design, participant features and main results of these trials have been reported (18–23); these were carried out in compliance with local regulations governing human research. In brief, participants were adults with documented sustained or

Abbreviations and Acronyms:
AF   = atrial fibrillation
CI   = confidence interval
INR   = international normalized ratio
RR   = relative risk
SPAF   = Stroke Prevention in Atrial Fibrillation
TIA   = transient ischemic attack

recurrent AF without mitral stenosis or prosthetic cardiac valves recruited from inpatient and outpatient facilities at two dozen clinical sites. Those under age 60 years without associated cardiovascular disease ("lone AF") and heavy alcohol users precluding safe anticoagulation were not eligible. Participants in the SPAF III trial assigned aspirin plus fixed, low-dose warfarin were included if the international normalized ratio (INR) did not exceed 1.4 during follow-up (mean achieved INR = 1.1, n = 290), because INRs below 1.5 offer minimal protection against ischemic stroke in patients with AF (18,24,25).

Atrial fibrillation was categorized as intermittent if sinus rhythm was documented within 12 months before study entry for SPAF I and II participants and within three months for SPAF III subjects. Diagnosis of intermittent AF required at least two electrocardiogram (ECG)-documented episodes before entry, no reversible cause of AF (e.g., thyrotoxicosis, pneumonia) and no iatrogenic cardioversion unless AF recurred before entry. For this analysis, those classified as intermittent AF with AF on the entry ECG and no subsequent documentation of sinus rhythm during the next six months were reclassified as sustained AF (n = 86; 16% of those initially classified as intermittent). When ischemic stroke occurred within the first six months after entry, the pattern of AF was classified based on observations before the stroke. Participants undergoing therapeutic cardioversion during the initial six months using drugs (n = 31) or countershock (n = 22) were included in the main analysis, except as otherwise specified. Hypertension was diagnosed if blood pressure exceeded either 160 mm Hg systolic or 90 mm Hg diastolic on repeated observations over six months or if chronic antihypertensive medication was required.

Patients were followed in clinic every three to six months to assess compliance and detect strokes. Stroke events were verified and categorized as cardioembolic, noncardioembolic or of uncertain cause by a central events committee unaware of treatment using a clinical classification scheme (26). A risk stratification scheme previously derived from this cohort by multivariate analysis was used to compare predictors of thromboembolism in patients with intermittent versus sustained AF (15).

Baseline characteristics of the intermittent versus sustained AF groups were compared using the Student *t* test for continuous variables and the chi-square test for categorical variables. The age-adjusted relative risk (RR) for stroke

Table 1. Clinical Features of Participants Based on Pattern of Atrial Fibrillation

	Intermittent AF (n = 460)	Sustained AF (n = 1,552)	p Value
Age (yrs), mean ± SD	66 ± 11	70 ± 9	< 0.001
Women, %	37	26	< 0.001
Alcohol use (≥14 drinks/week), %	6	9	0.02
Hypertension, %	49	54	n.s.
Diabetes mellitus, %	13	16	n.s.
Duration of AF <1 year, %	37	22	< 0.001
History of heart failure, %	11	21	< 0.001
Carotid surgery or bruit, %	4	5	n.s.
Peripheral arterial disease, %	4	7	0.009
Prior stroke or TIA, %	7	8	n.s.
Prior myocardial infarct, %	7	10	n.s.
Moderate-severe LV dysfunction, %	4	10	< 0.001

AF = atrial fibrillation; LV = left ventricular, qualitatively assessed by two-dimensional precordial echocardiography; n.s. = not significant (p ≥ 0.05); TIA = transient ischemic attack.

associated with a characteristic was estimated using a Cox proportional hazards model after first including the variable age. Differences in age-adjusted RRs between the intermittent and sustained AF patients were evaluated by fitting the model, adjusting for age, pattern of AF and factor of interest, and then testing significance of the interaction term for pattern of AF and factor of interest. Independent predictors of stroke were identified by a combination of forward and backward stepwise modeling techniques (Cox proportional hazards model). Statistical significance in each of these cases was assessed using the likelihood ratio statistic. Stroke rates were expressed per patient-year of observation, with 95% confidence intervals (CIs) determined from the Poisson distribution. Rates were compared between groups using a Poisson regression model. Analyses were done using SPSS and EGRET statistical software. All tests were two sided; statistical significance was accepted at the 95% confidence level (p < 0.05).

RESULTS

Among 2,012 SPAF participants receiving aspirin or aspirin plus inefficacious doses of warfarin, AF was classified as intermittent in 460 (23%). Those with intermittent AF (mean age 66 years) were, on average, four years younger than those with sustained AF (p < 0.001), were more often women (p < 0.001) and had lower frequencies of heart failure and peripheral arterial disease (Table 1). During the initial six months of observation, 72% of SPAF III partic-

Table 2. Factors Associated With Ischemic Stroke in Intermittent Versus Sustained AF: Age-adjusted Relative Risks*

	Intermittent AF			Sustained AF		
		Age-adjusted			Age-adjusted	
	n	RR	p Value	n	RR	p Value
Age per decade (yrs)	—	2.2	< 0.001	—	2.1	< 0.001
Women	168	1.3	n.s.	398	2.0	< 0.001
Hypertension	224	3.6	0.002	832	2.3	< 0.001
Diabetes mellitus	60	1.7	n.s.	244	1.7	0.04
Alcohol use (≥14 per week)	27	†	n.s.	145	0.4	0.03
Systolic blood pressure >160 torr	53	1.6	n.s.	139	4.0	< 0.001
Hormone use (n = 1,182)	41	2.2	n.s.	57	3.3	0.007
Carotid surgery or bruit	20	2.8	n.s.	77	1.4	n.s.
Prior stroke or TIA	31	4.5	0.007	128	3.2	< 0.001
Peripheral arterial disease	18	8.5	0.002	114	1.3	n.s.

*During aspirin therapy. Left atrial diameter by M-mode echocardiography averaged 4.3 cm among participants with intermittent AF with and without stroke.
†No strokes occurred in these 27 patients. The age-adjusted RR approaches zero, but no estimate for the upper bound of the 95% confidence interval is available for the model.
AF = atrial fibrillation; n.s. = not significant (p ≥ 0.05); RR = relative risk; TIA = transient ischemic attack.

ipants with intermittent AF had recurrent AF based on symptoms or rhythm tracings (comparable data not available for SPAF I and II).

During a mean follow-up of two years, the observed rate of ischemic stroke (n = 27) was 3.2% per year (95% CI 2.2 to 4.6) among those with intermittent AF compared with 3.3% per year (95% CI 2.7 to 4.0) for those with sustained AF. The exclusion of patients in whom cardioversion was attempted (4% of intermittent and 2% of sustained AF patients) did not alter the observed stroke rates.

Factors associated with ischemic stroke in patients with intermittent AF by univariate analysis were age (p < 0.001), hypertension (age-adjusted, p = 0.002), prior stroke or transient ischemic attack (TIA) (age-adjusted, p = 0.007) and peripheral arterial disease (age-adjusted, p = 0.002) (Table 2). Based on age-adjusted univariate analysis, systolic blood pressure >160 was more strongly associated with subsequent stroke in patients with sustained than intermittent AF (p = 0.06), while peripheral arterial disease was more closely related to stroke in patients with intermittent than sustained AF (p = 0.02). Age (p < 0.001), hypertension (p = 0.003) and prior stroke or TIA (p = 0.01) were the strongest predictors of ischemic stroke in patients with intermittent AF by multivariate analysis; these factors were also predictive among those with sustained AF (Table 3).

Applying the risk stratification scheme previously derived from the entire cohort, those with intermittent AF were more frequently classified as low risk than were those with sustained AF (p = 0.004, linear association), although differences were small (Table 4, Fig. 1). This scheme successfully stratified participants with intermittent AF based on observed stroke rates (Table 4, Fig. 2; p < 0.001). About one-fourth of those with intermittent AF had

high-risk features, and in these patients the rate of ischemic stroke was 7.8% per year (95% CI 4.5 to 14). Considering each category of predicted stroke risk by this scheme, there were no significant differences in observed stroke rates between those with intermittent and sustained AF (Table 4).

DISCUSSION

In this large cohort of patients treated with aspirin, intermittent AF was associated with stroke rates comparable with sustained AF. Predictors of ischemic stroke were also similar, and a single risk stratification scheme predicted stroke for patients with either pattern of AF. Nearly one-fourth of the cohort with intermittent AF was classified as high-risk, and their rate of ischemic stroke was substantial during treatment with aspirin.

Our results are at odds with studies reporting lower rates of stroke in patients with intermittent rather than sustained

Table 3. Independent Predictors of Ischemic Stroke in Patients With Intermittent and Sustained AF

	Intermittent AF (n = 460)		Sustained AF (n = 1,552)	
	Relative Risk	p Value	Relative Risk	p Value
Age per decade	2.1	< 0.001	1.7	< 0.001
Hypertension	3.4	0.003	1.8	0.008
Prior stroke or TIA	4.1	0.01	2.7	< 0.001
Female gender	—	n.s.	1.8	0.004
Systolic BP >160 torr	—	n.s.	2.8	< 0.001

AF = atrial fibrillation; BP = blood pressure; n.s. = not significant (p ≥ 0.05); TIA = transient ischemic attack.

Table 4. Risk Stratification for Ischemic Stroke: SPAF III Exploratory Analysis Criteria*

	Intermittent AF			Sustained AF		
Risk Stratum	n	Percent of Cohort	Observed Stroke Rate (95% CI)	n	Percent of Cohort	Observed Stroke Rate (95% CI)
High (Any of: age >75 and hypertension, age >75 and female, systolic BP >160 torr, prior stroke or TIA)	112	24	7.8 (4.5 to 14)	459	30	8.7 (6.8 to 11)
Moderate (Either of: hypertension and age ≤75 yr, diabetes; and no high-risk features)	148	32	3.8 (2.2 to 6.7)	530	34	2.3 (1.6 to 3.4)
Low (No moderate or high risk features)	200	43	0.8 (0.3 to 2.4)	563	36	1.0 (0.6 to 1.7)

*Derived from multivariate analysis combining participants with intermittent versus sustained AF from this cohort (15).
    AF = atrial fibrillation.

AF (1,3,10) and in line with case series showing no differences in stroke between recurrent intermittent and sustained AF (9,17,27). Patients younger than 60 years old with "lone" AF and those with a single documented episode of AF were not eligible for participation. Hence, our cohort differs importantly from those in which young patients with "lone" or isolated episodes were prevalent (3,4,9). The mean age of our cohort was similar to that of patients with intermittent AF seen in clinical practice (5,7,9). Previous studies also have identified concomitant hypertension (7,30) and age (7,9) as predictors of stroke in intermittent AF.

Treatment with adjusted-dose warfarin appears to reduce stroke similarly for patients with either intermittent or sustained AF, although data are limited. Among high-risk paticipants in the SPAF III trial categorized as intermittent AF, those given adjusted-dose warfarin had significantly (p = 0.01) fewer strokes (0 strokes/91 participants) than those given aspirin and low, inefficacious doses of warfarin (6 strokes/80 participants) (Pearce LA for the SPAF Investigators, personal communication).

Study limitations. Participants in the SPAF clinical trials were recruited mainly from in-patient, hospital-based populations and may not be representative of those with intermittent AF in the general population. Furthermore, our findings may not apply to younger, healthier and less symptomatic outpatients with intermittent AF. The risk of cardioembolic stroke associated with intermittent AF is likely to be related to the frequency and duration of paroxysms. The frequency and duration of episodes of AF were not accurately ascertained in this study, and stroke could not be reliably correlated with recurrence of the dysrhythmia or with conversion to sustained AF during follow-up (28). All participants in our study were given aspirin, which decreases ischemic stroke by about 20% in patients with AF (29).

Conclusions. Elderly people with recurrent intermittent AF in this cohort had rates of ischemic stroke comparable with those with sustained AF and shared risk factors for stroke. The risk of stroke varies widely among those with intermittent AF as it does for sustained AF, and our results suggest that stroke risk can be stratified using the same clinical features irrespective of the pattern of AF. Additional
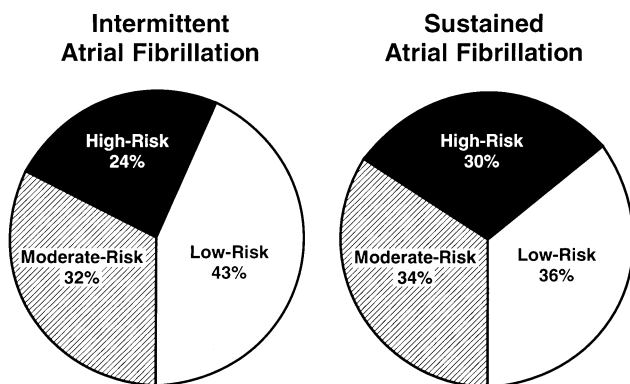

Figure 1. Distribution according to predicted stroke risk using the SPAF Exploratory Analysis Criteria for patients with intermittent (n = 460) versus sustained (n = 1552) atrial fibrillation.
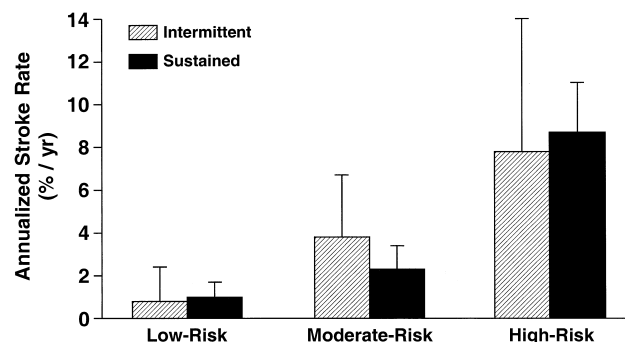

Figure 2. Observed rates of ischemic stroke according to risk category.

studies correlating the frequency and duration of paroxysms with stroke rates are needed. Selection of antithrombotic therapy to prevent stroke should be based on the estimated risk of thromboembolism both for patients with intermittent and sustained AF. Patients with intermittent AF and additional stroke risk factors have high rates of stroke and likely benefit from anticoagulation for stroke prevention.

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