AN ANALYSIS OF THE LOWEST EFFECTIVE INTENSITY OF PROPHYLACTIC ANTICOAGULATION FOR PATIENTS WITH NONRHEUMATIC ATRIAL FIBRILLATION

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ABSTRACT

Background To avert major hemorrhage, physicians need to know the lowest intensity of anticoagulation that is effective in preventing stroke in patients with atrial fibrillation. Since the low rate of stroke has made it difficult to perform prospective studies to resolve this issue, we conducted a case–control study.

Methods We studied 74 consecutive patients with atrial fibrillation who were admitted to our hospital from 1989 through 1994 after having an ischemic stroke while taking warfarin. For each patient with stroke, three controls with nonrheumatic atrial fibrillation who were treated as outpatients were randomly selected from the 1994 registry of the anticoagulant-therapy unit (222 controls). We used the international normalized ratio (INR) to measure the intensity of anticoagulation. For the patients with stroke, we used the INR at admission; for the controls, we selected the INR that was measured closest to the month and day of the matched case patient's hospital admission.

Results The risk of stroke rose steeply at INRs below 2.0. At an INR of 1.7, the adjusted odds ratio for stroke, as compared with the risk at an INR of 2.0, was 2.0 (95 percent confidence interval, 1.6 to 2.4); at an INR of 1.5, it was 3.3 (95 percent confidence interval, 2.4 to 4.6); and at an INR of 1.3, it was 6.0 (95 percent confidence interval, 3.6 to 9.8). Other independent risk factors were previous stroke (odds ratio, 10.4; 95 percent confidence interval, 4.4 to 24.5), diabetes mellitus (odds ratio, 2.9; 95 percent confidence interval, 1.3 to 6.5), hypertension (odds ratio, 2.5; 95 percent confidence interval, 1.1 to 5.7), and current smoking (odds ratio, 5.7; 95 percent confidence interval, 1.4 to 24.0).

Conclusions Among patients with atrial fibrillation, anticoagulant prophylaxis is effective at INRs of 2.0 or greater. Since previous studies have indicated that the risk of hemorrhage rises rapidly at INRs greater than 4.0 to 5.0, tight control of anticoagulant therapy to maintain the INR between 2.0 and 3.0 is a better strategy than targeting lower, less effective levels of anticoagulation. (N Engl J Med 1996;335: 540-6.)

ATRIAL fibrillation is a common risk factor for ischemic stroke, particularly among the elderly.[1] Randomized trials have demonstrated that a relatively low intensity of anticoagulant therapy can largely eliminate the risk of stroke attributable to atrial fibrillation.[2-8] In the trials, the rates of bleeding complications were acceptably low. However, there is concern that in actual medical practice the risk of hemorrhage associated with the use of anticoagulants, particularly among the elderly, may be higher than that in the initial group of randomized trials.[9,10] Since the risk of major hemorrhage in patients treated with anticoagulants rises steeply with the intensity of anticoagulation,[11-13] it would be valuable to determine the lowest effective intensity that still prevents ischemic stroke in patients with atrial fibrillation.

Ischemic strokes are rare among patients who are truly taking anticoagulant agents. For example, in the first five trials of anticoagulant therapy in patients with atrial fibrillation, there were a total of only 27 ischemic strokes in almost 1900 person-years of follow-up of patients randomly assigned to anticoagulant therapy, and 29 percent of the strokes occurred in patients who were not taking their assigned medication.[8] This low rate of events makes it difficult to conduct prospective studies to determine the relation between the level of anticoagulation as indicated by the international normalized ratio (INR) and the risk of stroke. We chose instead to use a case–control approach similar to that used in our previous study of intracranial hemorrhage among patients taking anticoagulant drugs.[12] In the present study, the case subjects were patients with atrial fibrillation who had ischemic strokes despite receiving anticoagulants, and the controls were patients with atrial fibrillation who did not have strokes and whose treatment was managed by our anticoagulant-therapy unit.

METHODS

Identification and Eligibility of Patients with Stroke

Using a log of consecutive patients discharged from Massachusetts General Hospital from January 1, 1989, through December

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31, 1994, we identified 669 patients with codes from the *International Classification of Diseases, Ninth Revision* (ICD-9)[14] that indicated discharge diagnoses of both atrial fibrillation (ICD-9 code 427.31) and ischemic stroke (codes 436.0, 434.91, 434.9, 434.11, 434.1, 434.01, 434.00, 434.0, 433.11, 433.01, and 432.9). We used January 1, 1989, as the starting date for the identification of patients discharged after hospitalization for ischemic stroke because 1989 was the first full year during which values for the international sensitivity index (ISI) were known for all the thromboplastin preparations used in the prothrombin-time assay at our hospital. The medical records of 6 of the 669 potentially eligible patients (1 percent) were not available for review.

The remaining 663 patients' medical records were reviewed to confirm that the patients were at least 18 years old, had a validated diagnosis of ischemic stroke occurring before admission, had electrocardiographic evidence of atrial fibrillation, and were taking warfarin at the time of the stroke. Patients with mitral stenosis or prosthetic heart valves were not eligible. Whether the patients were taking warfarin at the time of admission was determined from reviews of admission notes made by the resident and attending physicians. The diagnosis of ischemic stroke was confirmed by a clinical history of the sudden development of a major neurologic deficit lasting more than 24 hours that was correlated with a cerebrovascular territory. Seventy-four patients met the eligibility criteria. The vast majority of those excluded were not taking warfarin at the time of the stroke. In 64 cases, the diagnosis of ischemic stroke was confirmed by positive evidence of cerebral infarction on computed tomography (CT) or magnetic resonance imaging (MRI). In nine cases, the initial CT scan of the head showed no evidence of primary intracerebral hemorrhage and no follow-up CT or MRI study was performed. In one case, the diagnosis was based solely on the clinical presentation, which was typical of ischemic stroke.

Identification and Eligibility of Controls

All the controls were randomly selected from the 1994 registry of the hospital's anticoagulant-therapy unit. We chose 1994 because it was the first full year during which the results of all prothrombin-time tests performed at laboratories affiliated with the unit were expressed in terms of the INR. During 1994, this unit managed the treatment of 2680 patients, including approximately 700 with nonrheumatic atrial fibrillation. Three controls were matched to each patient with stroke. The medical records of the controls were reviewed to confirm that the controls were at least 18 years old, had nonrheumatic atrial fibrillation, and did not have a prosthetic heart valve. No patient served as a control for more than one patient with stroke.

To validate the use of controls treated in 1994, we examined the distribution of INR values for each of the study years for patients with nonrheumatic atrial fibrillation whose tests were performed at either the hospital laboratory or another large clinical laboratory serving patients managed by the unit. Together, these two laboratories accounted for nearly 55 percent of the prothrombin-time tests for patients whose treatment was managed by the unit. Throughout the study period (1989 through 1994), both laboratories kept records of the ISI values of the thromboplastin they used, thus allowing calculation of the INRs. For 1994, the distribution of INR values among all the patients with atrial fibrillation who were treated by the unit was essentially the same as the distribution of values in the subgroup of patients served by these two laboratories. Similarly, the distributions of INR values for patients with atrial fibrillation whose prothrombin times were determined by these two laboratories during 1989 through 1993 were not significantly different from the distribution for 1994. Our analyses indicated that the INR values of the control patients treated in 1994 were representative of the INR values of potential control patients from 1989 through 1994.

The mean INR was also consistent over time among the patients with stroke; in 1989 the mean INR was 1.62 (n = 11); in 1990, 1.58 (n = 6); in 1991, 1.49 (n = 14); in 1992, 1.87 (n = 10); in 1993, 1.41 (n = 16); and in 1994, 1.63 (n = 17). Logistic-regression models assessing year-specific relations between the INR and the occurrence of stroke were constructed for the subgroup of potential controls for whom INR values were available. A variable for calendar year did not have a significant effect in the model. The estimated odds ratios for stroke as a function of the INR that were generated by these models for each year fell within 1 SE of the odds ratios estimated by the model including the randomly selected 1994 controls (see the Results section).

Sources of Data

Data on the characteristics of the patients with stroke and their controls were obtained primarily from hospital records, with supplementation in a few instances from physicians' office records. The information recorded for each patient included the INR and the duration of warfarin therapy, race, sex, and a variety of clinical characteristics. Echocardiographic variables were also recorded, if available. For the patients with stroke, we included the staff neurologist's assessment of the likely mechanism and location of the stroke and the magnitude of the resulting neurologic deficit. For the controls, we recorded clinical data as of the time the selected INR was determined.

INRs were calculated on the basis of the prothrombin-time ratio (PTR) and the ISI of the thromboplastin used in the assay[15] as follows: $INR = PTR^{ISI}$. For the patients with stroke, we used the INR measured in blood drawn in the emergency room at admission. Since 1988, our hospital laboratory has used a thromboplastin with a known ISI (Simplastin Automated, Organon Teknika, Durham, N.C.); the ISI values for different lots range from 1.9 to 2.2. Two patients with stroke had the PTR measured at a referring hospital's emergency room. Both of these hospitals' laboratories were using Thromboplastin C (Dade, Baxter Diagnostics, Deerfield, Ill.) with an ISI of 2.7. For the controls, the INR determined on the date closest to the month and day of admission for the matched patient with stroke was obtained from the data base of the anticoagulant-therapy unit. Such a method of selecting INRs for the controls avoided the bias toward out-of-range values that is inherent in random selection of INR values (since more frequent INR testing is done when patients have out-of-range values) and accounts for possible seasonal changes in the INR.

Information on the duration of warfarin therapy was missing for four patients with stroke. Echocardiographic data were available for 91 percent of the patients with stroke and 88 percent of the controls (echocardiography was performed during the study period in 95 percent of the controls). All but seven of the echocardiograms (one in a patient with stroke and six in controls) were obtained at Massachusetts General Hospital. Data for patients with stroke and controls were otherwise complete.

Additional definitions used in the analysis included the following:

Nonrheumatic atrial fibrillation — electrocardiographically documented atrial fibrillation, with no evidence of mitral stenosis on echocardiography and no clinical history of mitral stenosis. For three patients with stroke, atrial fibrillation was first documented during the initial 48 hours of hospitalization for stroke. For the controls, atrial fibrillation was documented in the medical records before the date when the chosen INR was measured.

Paroxysmal atrial fibrillation — atrial fibrillation documented electrocardiographically at least once in the preceding 24 months, but with intervening periods of normal sinus rhythm.

Hypertension — a diagnosis of hypertension listed in the medical record. Ninety-four percent of the patients with stroke and 96 percent of the controls who had been given a diagnosis of hypertension were taking antihypertensive medication.

Diabetes mellitus — a diagnosis of diabetes mellitus listed in the medical record. Seventy-five percent of the patients with stroke and 64 percent of the controls who had been given a diagnosis of diabetes were being treated with insulin or oral hypoglycemic agents.

Mitral regurgitation — mild, moderate, or severe regurgitation as estimated from the echocardiogram.

Coronary artery disease — a history of myocardial infarction, bypass surgery, angioplasty, or angina.

Peripheral vascular disease — a history of intermittent claudication or revascularization surgery.

Prior stroke — a diagnosis of previous stroke recorded in the medical record. In all instances, previous strokes occurred before the beginning of anticoagulant therapy.

The research protocol for this study was reviewed and approved by the hospital's subcommittee on human studies.

Statistical Analysis

For univariate comparisons between the patients with stroke and the controls, we assessed statistical significance with the chi-square test or Fisher's exact test, as appropriate. Odds ratios with 95 percent confidence intervals were calculated by standard methods.[16,17] A continuous probability-density function for INRs among both the patients with stroke and the controls was constructed according to a nonparametric method (with the area under the curve between any two INRs used to give an estimate of the proportion of patients whose INRs fell between those values).[18] The ratio of the probability densities among the case patients to those among the controls, normalized to 1.0 at an INR of 2.0, provided a nonparametric estimate of the odds ratio for stroke at any given INR level as compared with an INR of 2.0.

We used logistic-regression models to assess the independent effect of multiple clinical characteristics on the risk of stroke. INRs were transformed with the natural logarithm to provide a better linear fit. Models that provided an increase in the risk of stroke below an INR of 2.0 but no change in the odds at 2.0 or higher were compared with models that included only a single linear term for the log INR. The latter models provided a lower log likelihood as well as estimates of the effect of the INR that were more consistent with the results of the univariate analysis and are therefore described in the Results section. Other predictive variables were chosen for inclusion in the logistic models because they were significantly associated with risk in the univariate analysis ($P<0.05$) or because they were significant in the pooled analysis of the trials of anticoagulant therapy in patients with atrial fibrillation.[8] Variables that were not found to be significant independent predictors of the risk of stroke were eliminated, and the model refitted. The results of the matched case–control analysis[19] differed negligibly from the estimates in the unmatched analysis; only the results of the unmatched analyses are presented here. Statistical analyses were performed with SAS (SAS Institute, Cary, N.C.), S-plus (Statistical Science, MathSoft, Seattle), and StatXact (Cytel Software, Cambridge, Mass.).

RESULTS

Clinical Course of Patients with Stroke

We identified a total of 74 patients who were admitted to our hospital from 1989 through 1994 with nonrheumatic atrial fibrillation and ischemic stroke who were taking warfarin at the time of the stroke (Table 1). Ninety-two percent of the patients had embolic stroke, 84 percent in the anterior circulation and 8 percent in the posterior circulation. Six patients (8 percent) were given a diagnosis of lacunar infarcts, three on the basis of CT scanning and three on the basis of MRI. Twenty percent of the patients with stroke died before discharge, and 19 percent survived with major neurologic deficits that prevented their return to independent living.

TABLE 1. CLINICAL CHARACTERISTICS OF 74 PATIENTS WITH ISCHEMIC STROKE.

CHARACTERISTIC	NO. (%)
Type of stroke	
Embolic	68 (92)
Anterior circulation	62 (84)
Posterior circulation	6 (8)
Lacunar	6 (8)
Ipsilateral carotid disease (≥50% stenosis or occlusion)*	5 (8)
Outcome†	
Death	15 (20)
Major neurologic deficit	14 (19)
Minor neurologic deficit	45 (61)

*Doppler ultrasonography of the carotid artery was not performed in eight patients.

†A major deficit was defined as a neurologic deficit that prevented independent living after discharge, and a minor deficit as less severe damage.

Comparison of Patients with Ischemic Stroke and Controls

A history of stroke was a powerful risk factor for stroke while receiving anticoagulant therapy (odds ratio, 6.8; 95 percent confidence interval, 3.9 to 12.1) (Table 2). Other factors that were statistically significant in the univariate analysis were age greater than 75 years, a history of peripheral vascular disease, a history of transient ischemic attacks, diabetes mellitus, and current smoking (Table 2). Coronary artery disease was of borderline significance. The patients with stroke and the controls did not differ significantly in terms of sex, race, the numbers with chronic as opposed to paroxysmal atrial fibrillation, the proportion with hypertension, and the proportion with congestive heart failure.

Among the echocardiographic features, mitral annular calcification and left ventricular hypertrophy were found more frequently among the patients with stroke. Left atrial size had no relation to the risk of stroke. The vast majority of both patients with stroke and controls had left ventricular ejection fractions of at least 40 percent, making it difficult to determine whether very low ejection fractions were associated with stroke (Table 2).

The INR was a powerful determinant of the risk of stroke (Fig. 1). The risk rose very steeply as INR values fell below 2.0. As compared with patients with INRs of 2.0, those with INRs of 1.7 had nearly twice the risk of stroke; those with INRs of 1.5 had nearly three times the risk of patients whose INRs were 2.0, and those with INRs of 1.3 had a sevenfold greater risk (Fig. 1).

The effect of the INR on the risk of stroke changed little when other correlates of stroke were also included in multiple logistic models (Table 3). Table 4 shows the adjusted odds ratios for stroke at INR values from 1.0 to 2.0, as estimated in the model.

Among other independent determinants of the risk of stroke, having had a previous stroke was particularly strong. Diabetes mellitus, hypertension, and current smoking were also significant risk factors for stroke (Table 3). There were no statistically significant interactions between any of these factors and the INR. In particular, there was no evidence that the relation between the INR and the relative risk of stroke differed between patients who had had a prior stroke and those who had not had a stroke.

Patients with Stroke and Controls Who Were Treated at the Anticoagulant-Therapy Unit

Fifty-three patients with ischemic stroke had their warfarin therapy managed by the staff of the hospital's anticoagulant-therapy unit. The effects of previously identified independent risk factors for ischemic stroke were largely unchanged in analyses restricted to these patients and their controls. The odds ratio for stroke among patients with a 50 percent lower INR was 15.8 (95 percent confidence interval, 6.6 to 37.9); among patients with a prior stroke as compared with those without a prior stroke, the odds ratio was 7.1 (95 percent confidence interval, 2.8 to 17.7); for current smoking, it was 5.1 (95 percent confidence interval, 1.1 to 24.5); for diabetes mellitus, 2.5 (95 percent confidence interval, 1.1 to 6.1); and for hypertension, 2.0 (95 percent confidence interval, 0.8 to 4.8).

TABLE 2. CHARACTERISTICS OF PATIENTS WITH ISCHEMIC STROKE AND CONTROLS.

CHARACTERISTIC	PATIENTS WITH ISCHEMIC STROKE (N = 74)	CONTROLS (N = 222)	ODDS RATIO (95% CI)*
	percent		
Male sex	43	51	0.7 (0.4–1.2)
Race			
White†	95	94	1.0
Other	5	6	0.9 (0.2–3.1)
Age >75 years	64	49	1.8 (1.1–3.1)
Atrial fibrillation			
Chronic†	69	71	1.0
Paroxysmal	31	29	1.1 (0.6–1.9)
Congestive heart failure	19	18	1.1 (0.6–2.2)
Coronary artery disease	43	30	1.8 (1.0–3.0)
Cancer	4	5	0.9 (0.2–3.6)
Diabetes mellitus	34	18	2.3 (1.3–4.2)
Hypertension	68	63	1.2 (0.7–2.1)
History of peripheral vascular disease	26	10	3.0 (1.5–5.8)
Current smoking‡	10	3	4.0 (1.3–12.3)
History of stroke	49	12	6.8 (3.9–12.1)
History of transient ischemic attacks	20	9	2.6 (1.2–5.4)
Duration of warfarin therapy			
≤1 mo	4	14	0.3 (0.1–0.9)
>1 mo†	96	86	1.0
Echocardiographic characteristic§			
Left atrial size			
<44 mm†	51	49	1.0
≥44 mm	49	51	1.1 (0.6–1.8)
Left ventricular akinesis	18	14	1.3 (0.6–2.8)
Left ventricular ejection fraction			
≥40%†	84	87	1.0
30–39%	7	10	0.8 (0.3–2.2)
<30%	9	4	2.7 (0.9–8.4)
Left ventricular hypertrophy	24	14	1.9 (1.0–3.7)
Mitral annular calcification	62	46	2.0 (1.1–3.4)
Mitral regurgitation	59	52	1.3 (0.7–2.3)
Aortic calcific stenosis	11	8	1.3 (0.5–3.4)

*Odds ratios are the odds of ischemic stroke among patients with the factor in question as compared with the patients without it. CI denotes confidence interval.

†Patients with this variable served as the reference group.

‡Data on smoking status were missing for 9 percent of the patients with stroke and 5 percent of the controls.

§Echocardiographic data were missing for 9 percent of the patients with stroke and 12 percent of the controls.

DISCUSSION

The randomized trials that demonstrated that anticoagulant therapy is strikingly effective in preventing stroke in patients with atrial fibrillation used a range of target levels of anticoagulation.[2-8] Anticoagulant agents were as effective in trials that used the lowest target intensities as in those using higher target levels.[2,6] These results, along with reports of the efficacy of very low doses of anticoagulant agents in preventing thrombosis in patients with other clinical conditions,[20,21] encouraged the belief that anticoagulation at a barely detectable intensity might be effective in patients with atrial fibrillation. Anticoagulant therapy with a very low target INR (e.g., <1.5) is currently being tested in at least two randomized trials.[22,23] Our results argue strongly against the efficacy of such very-low-intensity regimens.

We observed a steep increase in the risk of stroke as INR values fell below 2.0. The risk of stroke doubled as the INR decreased from 2.0 to 1.7, and it more than doubled again when the INR was reduced to 1.4. In contrast, INR values greater than 2.0 conferred little additional efficacy — beyond that of therapy at an INR of 2.0 — in preventing ischemic strokes.

The case–control design of our study gave it substantial statistical power to assess an uncommon outcome — ischemic stroke among patients with atrial fibrillation who were actually taking anticoagulants. On the basis of the event rates observed in randomized trials,[7,8] our case–control study had statistical power equivalent to that conferred by approximately 6000 person-years of prospective follow-up. We were able to determine the relation between the risk of stroke and a patient's INR at the time of the stroke. By contrast, randomized trials assess the efficacy of a

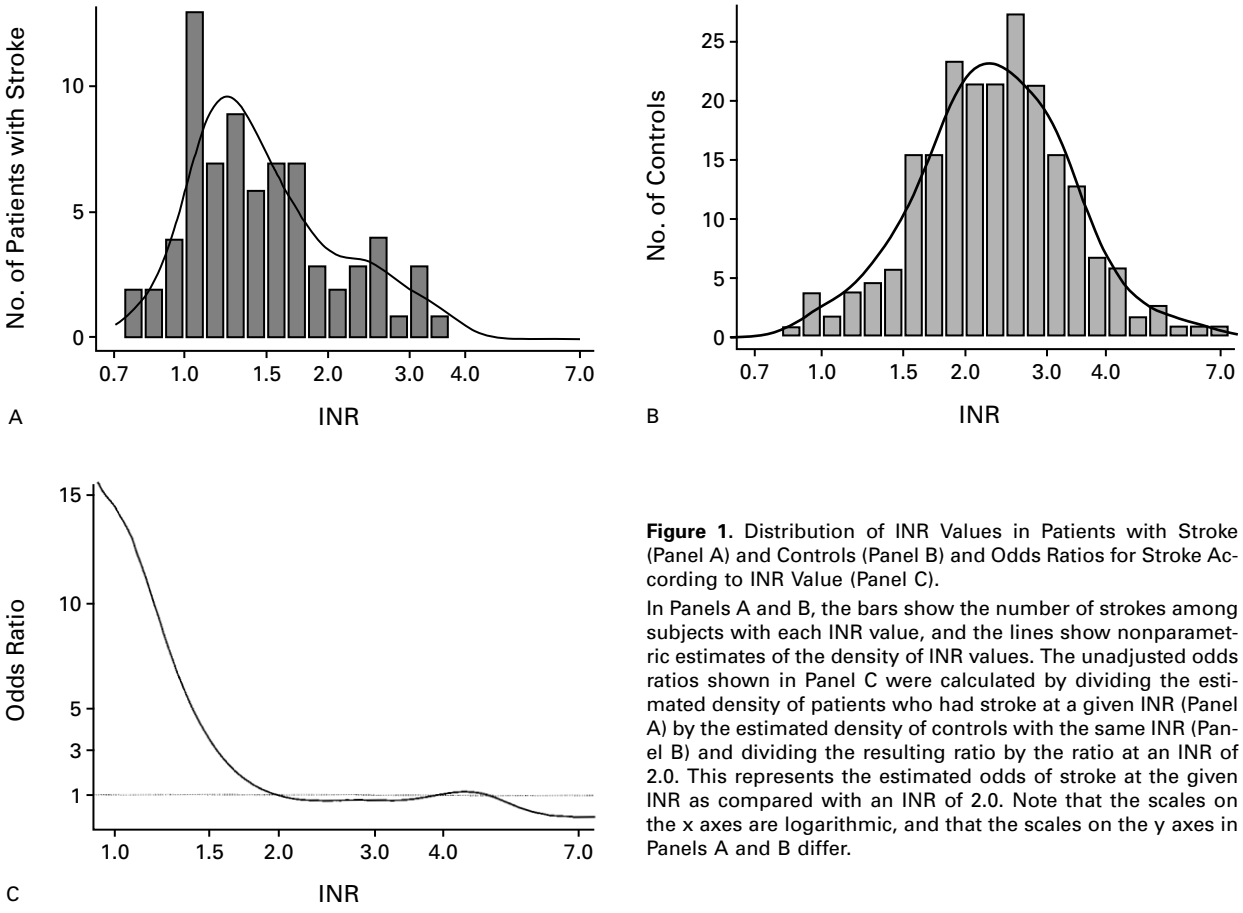

Figure 1. Distribution of INR Values in Patients with Stroke (Panel A) and Controls (Panel B) and Odds Ratios for Stroke According to INR Value (Panel C).

In Panels A and B, the bars show the number of strokes among subjects with each INR value, and the lines show nonparametric estimates of the density of INR values. The unadjusted odds ratios shown in Panel C were calculated by dividing the estimated density of patients who had stroke at a given INR (Panel A) by the estimated density of controls with the same INR (Panel B) and dividing the resulting ratio by the ratio at an INR of 2.0. This represents the estimated odds of stroke at the given INR as compared with an INR of 2.0. Note that the scales on the x axes are logarithmic, and that the scales on the y axes in Panels A and B differ.

target INR range; the results of such trials depend on whether those targets are achieved consistently. Secondary analyses of data from randomized trials investigating the relation between actual INR values and the rate of occurrence of stroke are a form of nonrandomized, prospective cohort study within the randomized trial. Using such an analysis, the European Atrial Fibrillation Trial Study Group concluded that an INR below 2.0 conferred less protection against stroke than an INR of 2.0 or higher.[24] This conclusion was based on only seven thromboembolic events in patients with INRs below 2.0 and was restricted to patients who had had a previous stroke or transient ischemic attack. In our study there were 58 events in patients with INRs below 2.0, allowing us to calculate specific odds ratios for stroke for the entire range of INR values from 1.0 to 2.0. We included both subjects who had had a prior stroke and those who had not.

Although our primary goal was to define the relation between the INR and the risk of ischemic stroke, our study design allowed us to explore the role of other clinical factors. Like most other studies of the risk of stroke in patients with atrial fibrillation, our study identified a history of stroke as a marker for substantially increased risk. Diabetes mellitus and hypertension were also independent risk factors for stroke, nearly tripling the risk. Our findings regarding these risk factors were similar to the results of the pooled analysis of the initial studies of patients with atrial fibrillation.[8] Our findings differed from those of the pooled analysis in two ways, however. First, we found no independent effect of age, although an age greater than 75 years was a significant risk factor in our univariate analysis. Second, we found current smoking to be a strong risk factor for stroke, although the small number of smokers made our estimates imprecise. Population-based studies have repeatedly found current smoking to be a risk factor for stroke.[25,26]

The primary methodologic concern with respect to case–control studies is selection bias — that is, in this study, the concern that patients with stroke may have been selected because their INR was low or that controls may have been selected because their INR was relatively high. The structure of our study reduced the possibility of such bias. The case subjects were the entire group of eligible patients admitted to our hospital from 1989 through 1994. The controls were randomly selected from the group

TABLE 3. INDEPENDENT RISK FACTORS FOR ISCHEMIC STROKE IN PATIENTS WITH NONRHEUMATIC ATRIAL FIBRILLATION WHO WERE TAKING WARFARIN.

RISK FACTOR	ODDS RATIO (95% CI)*
50% reduction in INR†	17.6 (7.9–39.3)
Previous stroke	10.4 (4.4–24.5)
Current smoking	5.7 (1.4–24.0)
Diabetes mellitus	2.9 (1.3–6.5)
Hypertension	2.5 (1.1–5.7)

*Odds ratios are the odds of ischemic stroke among patients with the factor in question as compared with the patients without it. CI denotes confidence interval.

†The odds ratio estimates the relative risk of stroke associated with a 50 percent reduction in the INR (e.g., from 2.0 to 1.0).

TABLE 4. ADJUSTED ODDS RATIOS FOR ISCHEMIC STROKE ACCORDING TO THE INR.

INR	ODDS RATIO (95% CI)*
1.0	17.6 (7.9–39.3)
1.1	11.9 (6.0–23.8)
1.2	8.3 (4.6–15.0)
1.3	6.0 (3.6–9.8)
1.4	4.4 (2.9–6.6)
1.5	3.3 (2.4–4.6)
1.6	2.5 (1.9–3.3)
1.7	2.0 (1.6–2.4)
1.8	1.5 (1.4–1.7)
1.9	1.2 (1.2–1.3)

*Odds ratios are the odds of ischemic stroke among patients with the INR in question as compared with the patients with an INR of 2.0. CI denotes confidence interval.

of all patients with atrial fibrillation whose treatment was managed by our anticoagulant-therapy unit in 1994, the first calendar year when INR values were available for all patients. Furthermore, our findings were essentially unchanged when the analysis was restricted to patients with stroke whose treatment had been managed by the anticoagulant-therapy unit, a fact that argues against the existence of referral bias.

Our earlier work indicated that the risk of intracranial hemorrhage in patients receiving warfarin increased exponentially at INR values above 4.0.[12] Cannegieter et al. observed a steep increase in the risk of intracranial hemorrhage at an INR of 5.0.[15] For patients with atrial fibrillation, anticoagulant prophylaxis is effective at INRs above 2.0, and safety is preserved at INRs lower than 4.0. The risk of either ischemic stroke or intracranial hemorrhage rises very steeply beyond these boundaries.

Surveys indicate that many physicians use low target INRs (such as 1.5) for elderly patients with atrial fibrillation in order to reduce what they perceive as a high risk of bleeding.[27] Our results suggest that greater efforts at tight control of the INR would have a better effect on health than using anticoagulant therapy at an ineffectively low intensity. Such efforts would include more widespread use of anticoagulant-therapy units and dosing algorithms that might require more frequent, rather than less frequent, measurements of the INR. Innovations such as having patients test their own INR levels could reduce the burden of frequent testing.[28]

Anticoagulant therapy in patients with atrial fibrillation is among the most effective preventive interventions in older adults, from the perspective of both health and cost.[29] To optimize the use of anticoagulants, the target INR needs to be both high enough to prevent ischemic stroke and low enough to avert major hemorrhage. The current standard target — an INR between 2.0 and 3.0 — was established by consensus on the basis of the results of randomized trials.[30] The empirical evidence for this recommendation was limited, however, since several of the trials did not even use an INR target. We are now accumulating better evidence of the true therapeutic range of anticoagulation in patients with atrial fibrillation. This range appears to extend from an INR of 2.0 to nearly 4.0, and indeed it includes the current INR standard of 2.0 to 3.0. The key to realizing the great potential benefit of anticoagulant therapy in patients with atrial fibrillation is to develop management strategies that keep the level of anticoagulation, as indicated by the patients' INR values, consistently within the range of 2.0 to 3.0.

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