

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 11, 2003

VOL. 349 NO. 11

Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation

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ABSTRACT

BACKGROUND

The incidence of stroke in patients with atrial fibrillation is greatly reduced by oral anticoagulation, with the full effect seen at international normalized ratio (INR) values of 2.0 or greater. The effect of the intensity of oral anticoagulation on the severity of atrial fibrillation-related stroke is not known but is central to the choice of the target INR.

METHODS

We studied incident ischemic strokes in a cohort of 13,559 patients with nonvalvular atrial fibrillation. Strokes were identified through hospitalization data bases and validated on the basis of medical records, which also provided information on the use of warfarin or aspirin, the INR at admission, and coexisting illnesses. The severity of stroke was graded according to a modified Rankin scale. Thirty-day mortality was ascertained from hospitalization and mortality files.

RESULTS

Of 596 ischemic strokes, 32 percent occurred during warfarin therapy, 27 percent during aspirin therapy, and 42 percent during neither type of therapy. Among patients who were taking warfarin, an INR of less than 2.0 at admission, as compared with an INR of 2.0 or greater, independently increased the odds of a severe stroke in a proportional-odds logistic-regression model (odds ratio, 1.9; 95 percent confidence interval, 1.1 to 3.4) across three severity categories and the risk of death within 30 days (hazard ratio, 3.4; 95 percent confidence interval, 1.1 to 10.1). An INR of 1.5 to 1.9 at admission was associated with a mortality rate similar to that for an INR of less than 1.5 (18 percent and 15 percent, respectively). The 30-day mortality rate among patients who were taking aspirin at the time of the stroke was similar to that among patients who were taking warfarin and who had an INR of less than 2.0.

CONCLUSIONS

Among patients with nonvalvular atrial fibrillation, anticoagulation that results in an INR of 2.0 or greater reduces not only the frequency of ischemic stroke but also its severity and the risk of death from stroke. Our findings provide further evidence against the use of lower INR target levels in patients with atrial fibrillation.

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N Engl J Med 2003;349:1019-26.

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NONVALVULAR ATRIAL FIBRILLATION increases the risk of ischemic stroke by a factor of five, presumably by an atrioembolic mechanism.¹⁻⁴ Such cardioembolic strokes are more severe than other types of ischemic stroke.⁵⁻⁸ Consistent with these observations are data from numerous population-based studies showing that mortality rates are higher for strokes associated with atrial fibrillation.⁹⁻¹⁵ Randomized trials have shown that warfarin is highly effective in preventing stroke in patients with atrial fibrillation, most likely by minimizing the formation of atrial thrombi.^{4,16,17} The full efficacy of anticoagulation is seen only at an international normalized ratio (INR) of 2.0 and above.^{18,19} Although the effect of oral anticoagulants on the frequency of stroke is clear, their effect on the severity of stroke and stroke-related mortality among patients with atrial fibrillation has been less well studied.^{8,20} In particular, the effect of the INR on the severity of stroke in such patients is unknown. We assessed the effect of the intensity of anticoagulation on the severity of ischemic stroke and on the 30-day mortality rate after stroke in a large cohort of patients with nonvalvular atrial fibrillation. We also determined the rates of ischemic stroke and intracranial hemorrhage according to the intensity of anticoagulation to help physicians and patients make better-informed decisions regarding optimal INR values.

METHODS

STUDY POPULATION

The study cohort has been described previously.²¹ We identified all patients 18 years or older enrolled in Kaiser Permanente of Northern California, a large, integrated health care system, who had nonvalvular atrial fibrillation between July 1, 1996, and December 31, 1997. Nonvalvular atrial fibrillation was identified on the basis of physician-assigned diagnoses of atrial fibrillation during a routine visit (International Classification of Diseases, 9th revision, Clinical Modification [ICD-9-CM], code 427.31), electrocardiographic data bases, or both.²² Patients with diagnosed mitral stenosis or heart-valve repair or replacement, transient perioperative atrial fibrillation, or recent hyperthyroidism were excluded. The final cohort included 13,559 patients.

DEFINITION AND IDENTIFICATION OF EVENTS

From each patient's index date through August 31, 1999, we identified ischemic strokes by searching

comprehensive automated hospitalization and billing-claims data bases for primary ICD-9-CM discharge diagnoses for ischemic stroke (codes 433.00 to 433.01, 433.10 to 433.11, 433.20 to 433.21, 433.30 to 433.31, 434.00 to 434.01, 434.10 to 434.11, 434.90 to 434.91, and 436.0).²² Medical records were reviewed by a clinical-outcomes committee of three physicians using a formal protocol. Cranial computed tomographic scans or magnetic resonance imaging studies (or both) were available for 98 percent of the patients. A validated ischemic stroke was defined as a neurologic deficit of sudden onset that persisted for more than 24 hours, corresponded to a vascular territory in the absence of primary hemorrhage, and was not explained by other causes (e.g., trauma, infection, or vasculitis). Patients with strokes that occurred during hospitalization or as a complication of a procedure were excluded. Patients who were evaluated in the emergency room and then discharged were included if there was evidence that the neurologic deficit had persisted for more than 24 hours. All events had to be independently verified by two committee members. Disagreements were resolved by a consensus of all three committee members. Any remaining disagreements were adjudicated by a consulting neurologist.

CHARACTERISTICS OF THE PATIENTS

Information on clinical variables, obtained from medical charts, included a history of ischemic stroke; a history of cerebrovascular disease, defined by known carotid or vertebralbasilar atherosclerosis or prior carotid endarterectomy; congestive heart failure; coronary artery disease; diabetes mellitus; hypertension; and acute in-hospital treatment with anticoagulants or thrombolytic therapy. Data on age, sex, and racial or ethnic group were obtained from administrative data bases.²¹

ANTITHROMBOTIC MEDICATION AND INR AT ADMISSION

The use of warfarin or aspirin at the time of the outpatient stroke was determined from a review of emergency-room and hospital-admission notes. The INR value at the time of presentation was recorded. The use of warfarin or aspirin was explicitly noted in the medication list obtained at admission in the case of 95 percent of patients. Documentation was incomplete for 28 patients. We subsequently determined that five of these patients had used warfarin on the basis of serial outpatient prescriptions for warfarin recorded in the pharmacy data base of the

health plan or recording of INR values up to the time of the stroke in the laboratory data base (or both). We categorized the 23 remaining patients as taking neither warfarin nor aspirin. The INR value at admission was missing for 10 of the 201 patients who were taking warfarin when they were admitted for an ischemic stroke. For two of these patients, we used an outpatient INR value determined within 72 hours before the event. The remaining eight patients were excluded. The antecedent level of anticoagulation control was assessed by calculation of the mean INR for each patient during the six months before the stroke. Ninety-three percent of the patients who had been taking warfarin had such prestroke INR values available.

SEVERITY OF STROKE AND 30-DAY MORTALITY

Because the focus of our study was the effect of prior oral anticoagulant therapy on the severity of stroke, we excluded 14 patients who had an intracerebral hemorrhage after in-hospital treatment with thrombolytic or heparin therapy for their stroke (3 were taking aspirin on admission, 5 were taking warfarin and had an INR of less than 2.0, and 6 were taking neither aspirin nor warfarin). No patient whose INR was 2.0 or greater on admission had a spontaneous intracerebral hemorrhage after the stroke.

We used the modified Rankin scale adapted by the Oxfordshire Community Stroke Project to classify the functional deficit at hospital discharge, on the basis of a physician's review of the medical record.²³ Patients with a score of 1 or 2 were classified as having minor strokes with a residual neurologic deficit that did not interfere with independent living. Patients with a score of 3 or 4 were classified as having major strokes with residual neurologic impairment that prevented independent living. A score of 5 denoted a severe stroke that resulted in total dependence and was usually associated with depressed consciousness. Clinical information was insufficient to determine the extent of the neurologic deficit at discharge for 15 patients (3 patients had been taking aspirin at admission, 2 had been taking warfarin and had an INR of less than 2.0, and 10 had been taking neither aspirin nor warfarin). These 15 patients were excluded from the analyses of the severity of stroke but were included in the analyses of 30-day mortality. We did not formally assess the mechanism of stroke.³

Death from any cause during hospitalization was

ascertained by a review of the medical charts, and deaths that occurred after discharge were identified by a review of the health plan's records and the California death registry.²⁴ Thirty-day follow-up data on vital status were complete.

RATES OF ISCHEMIC STROKE AND INTRACRANIAL HEMORRHAGE ACCORDING TO THE INTENSITY OF ANTICOAGULATION

We have previously reported on the effect of warfarin treatment on stroke rates in our cohort.²⁵ Here, we report on the incidence of ischemic stroke and intracranial hemorrhage according to the INR among patients who were taking anticoagulant agents. We focus on intracranial hemorrhage because it is the category of hemorrhagic toxicity that approximates ischemic stroke in terms of clinical and functional effect. The duration of treatment within designated INR ranges was calculated with use of an adapted linear interpolation method.²⁶ Warfarin status was assigned with use of a previously described algorithm incorporating pharmacy prescription information with laboratory INR data.²¹ To minimize error in interpolation, gaps in INR measurement exceeding 56 days were excluded. Events that occurred during these periods were not included in the INR-specific analyses of event rates.

STATISTICAL ANALYSIS

The severity of stroke was categorized according to the extent of the neurologic deficit at discharge: severe deficit (or in-hospital death), major deficit, or minor or no deficit. The correlation between categories of stroke severity and 30-day mortality was assessed with use of the Mantel-Haenszel chi-square trend test.²⁷ We used proportional-odds ordinal logistic-regression models that allowed us to compare multiple outcome categories in order to assess the independent effect of antithrombotic treatment on the severity of stroke at hospital discharge.²⁸ This approach fits a uniform log cumulative odds of progression across our three categories of severity as a function of antithrombotic therapy at admission and other covariates. The independent effect of antithrombotic therapy on 30-day mortality was assessed with the use of Cox proportional-hazards regression models.²⁹ The proportional odds and the proportional-hazards assumptions were met for these regression models. Kaplan-Meier survival curves were constructed for the 30-day period af-

Table 1. Clinical Characteristics of 596 Patients with Nonvalvular Atrial Fibrillation Who Had an Ischemic Stroke, According to the Antithrombotic-Medication Status at Admission.*

Characteristic	None (N=248)	Aspirin (N=160)	Warfarin (N=188)
Age (yr)			
Mean	79	80	76
Range	50–98	53–98	54–94
Female sex (%)	55	61	48
Cerebral atherosclerosis (%)	2	7	4
Heart failure (%)	35	35	39
Coronary heart disease (%)	30	32	36
Diabetes mellitus (%)	23	21	33
Hypertension (%)	70	58	70
Prior ischemic stroke (%)	22	27	40
International normalized ratio			
Median	NA	NA	1.7
25th–75th Percentile			1.3–2.2

* NA denotes not applicable.

Table 2. Severity of the Neurologic Deficit at Discharge and 30-Day Mortality Rates, According to the Antithrombotic-Medication Status and International Normalized Ratio (INR) at Admission.

Variable	None (N=248)	Aspirin (N=160)	Warfarin	
			INR <2.0 (N=117)	INR ≥2.0 (N=71)
			percent	
Severity and outcome of stroke				
Fatal in-hospital stroke	14	6	9	1
Severe stroke, total dependence	8	7	6	4
Major stroke, neurologic deficit that prevented independent living	37	36	44	38
Minor stroke, neurologic deficit that did not prevent independent living	36	49	38	55
No neurologic sequelae	5	2	3	2
Total 30-day mortality	24	15	16	6

ter stroke for the four antithrombotic medication groups, and these groups were compared with use of the log-rank test.²⁹

The study was approved by the institutional review boards at the Kaiser Permanente Medical Care Program of Northern California and at Massachusetts General Hospital. Because of the nature of the study, the requirement for informed consent was waived.

RESULTS

BASE-LINE CLINICAL FEATURES

During the study period, 618 patients with atrial fibrillation and ischemic stroke were identified. Twenty-two were excluded from the analysis: 8 because of missing INR values at admission and 14 because they had an intracerebral hemorrhage after thrombolytic or heparin therapy for their stroke. Of the remaining 596 patients, 188 (32 percent) were taking warfarin at the time of their stroke, 160 (27 percent) were taking aspirin, and 248 (42 percent) were taking neither warfarin nor aspirin (Table 1). Overall, the mean age of the patients was 78 years, and 55 percent were women. Approximately one third of the patients had a history of congestive heart failure, coronary heart disease, or stroke. Nearly 70 percent had hypertension. The warfarin group had a slightly lower mean age than the other two groups, had fewer women, and had a higher prevalence of congestive heart failure, coronary heart disease, diabetes mellitus, and prior stroke. The median INR on admission was 1.7 in the warfarin group, and 62 percent of these values were less than 2.0. The antecedent level of anticoagulation control was nearly identical for patients with an INR of 2.0 or greater at the time of admission and those with an INR of less than 2.0, with a median INR of 2.2 in both groups.

SEVERITY OF STROKE AND 30-DAY MORTALITY

The severity of stroke was strongly correlated with 30-day mortality ($P < 0.001$). Thirty-nine percent of patients with a severe stroke died within 30 days after discharge, as compared with 13 percent of those with a major deficit, 1 percent of those with a minor deficit, and none of those without neurologic sequelae.

INTENSITY OF ANTICOAGULATION AND SEVERITY OF STROKE

Among patients taking warfarin, 15 percent of those with an INR of less than 2.0 either died before discharge or were discharged after having a severe stroke, as compared with 5 percent of patients who had an INR of 2.0 or greater at presentation (Table 2). The proportion of patients who had a severe or fatal stroke did not differ significantly between those with an admission INR of 1.5 to 1.9 and those with an INR of less than 1.5. Twenty-two percent of patients who were not taking antithrombotic medication at the time of the stroke died before discharge or were discharged with a severe

deficit, as compared with 13 percent of those taking aspirin.

After adjustment for potential confounders in the proportional-odds model, the medication group remained an independent risk factor for the severity of stroke when patients who had an INR of 2.0 or greater were compared with those who had an INR of less than 2.0 or those who were taking neither aspirin nor warfarin (Table 3).

INTENSITY OF ANTICOAGULATION AND 30-DAY MORTALITY

The 30-day mortality rate among patients who were taking neither warfarin nor aspirin when they had an ischemic stroke was 24 percent (Table 2 and Fig. 1). Among patients who were taking warfarin at the time of the stroke and who had an INR of 2.0 or greater, 6 percent died within 30 days, as compared with 16 percent of those with an INR of less than 2.0. The 30-day mortality rate was essentially the same among patients who were admitted with an INR between 1.5 and 1.9 and those with an INR of less than 1.5 (18 percent and 15 percent, respectively). The 30-day mortality rate among patients who were taking aspirin when they had a stroke was 15 percent, which was nearly identical to the rate among patients who were taking warfarin and whose INR was less than 2.0.

As compared with an INR of 2.0 or greater, an INR of less than 2.0 at the time of stroke conferred an adjusted relative hazard of 3.4 for death within 30 days (95 percent confidence interval, 1.1 to 10.1) (Table 4). Patients who were taking neither warfarin nor aspirin at the time of the stroke had the highest hazard ratio for 30-day mortality (4.9), as compared with those who were taking warfarin and who had an INR of 2.0 or greater. Among patients who were taking aspirin, the hazard ratio was 2.5, but the confidence interval included a hazard ratio of 1.0. Other independent risk factors for 30-day mortality included older age, congestive heart failure, and diabetes mellitus (Table 4).

INTENSITY OF ANTICOAGULATION AND RATES OF STROKE AND INTRACRANIAL HEMORRHAGE

To provide a more comprehensive accounting of the clinical sequelae of various INR values, we calculated the incidence rates of ischemic stroke and intracranial hemorrhage according to the INR among the patients who were taking warfarin (Table 5). The rate of ischemic stroke was highest at INR values

Table 3. Independent Predictors of the Severity of Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation.*

Risk Factor	Odds Ratio (95% CI)	P Value
Antithrombotic medication at admission		
Neither aspirin nor warfarin	2.2 (1.3–3.8)	0.004
Aspirin	1.3 (0.7–2.3)	0.40
Warfarin, INR <2.0	1.9 (1.1–3.4)	0.03
Warfarin, INR \geq 2.0†	1.0	—
Age (per decade)	1.5 (1.2–1.8)	<0.001
Female sex	1.1 (0.8–1.5)	0.54
Heart failure	1.6 (1.1–2.2)	0.009
Coronary heart disease	1.1 (0.8–1.5)	0.59
Diabetes mellitus	1.3 (0.9–1.9)	0.18
Hypertension	1.2 (0.9–1.7)	0.24
Prior ischemic stroke	1.1 (0.8–1.5)	0.71

* The severity of stroke at hospital discharge was assessed with use of a modified Rankin scale and was categorized as follows: minor stroke with no neurologic sequelae or a deficit that did not interfere with independent living, major stroke with residual neurologic impairment that prevented independent living, or severe stroke that resulted in death in the hospital or total dependence after discharge. Estimates of effect were calculated with the use of proportional-odds logistic-regression models. These models compared severe plus major strokes with minor strokes and also compared severe strokes with major plus minor strokes. All variables are dichotomous except for age. CI denotes confidence interval, and INR international normalized ratio.

† This group served as the reference group.

of less than 2.0, especially values of less than 1.5. By contrast, there was no marked absolute increase in the rate of intracranial hemorrhage at INR values of less than 4.0.

DISCUSSION

Prior studies have demonstrated that the incidence of ischemic stroke among patients with atrial fibrillation is greatly reduced by warfarin therapy that results in an INR of at least 2.0, a relation confirmed by our results.^{18,19} We also found that an INR of 2.0 or greater markedly reduces the severity of stroke and the short-term mortality rate. Patients with atrial fibrillation and an INR of less than 2.0 who had an ischemic stroke faced a risk of death within 30 days that was more than three times the risk among patients with an INR of 2.0 or greater. The outcomes were essentially equally poor among warfarin users with an INR of 1.5 to 1.9 at admission and those with an admission INR of less than 1.5. The outcome was even worse for those who were receiving

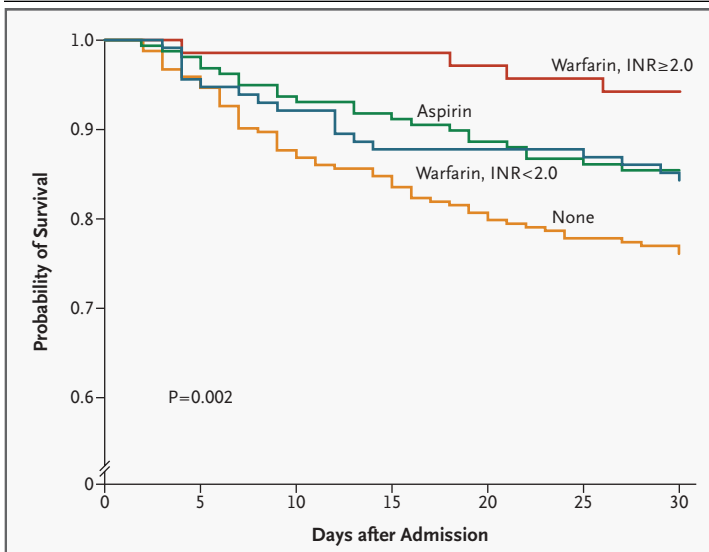


Figure 1. Kaplan–Meier Estimates of Survival in the 30 Days after an Ischemic Stroke among Patients with Nonvalvular Atrial Fibrillation, According to the Antithrombotic-Medication Status at Admission.

Patients who were taking warfarin are separated into two groups: those with an international normalized ratio (INR) of less than 2.0, and those with an INR of 2.0 or greater. The P value refers to the overall difference among the groups.

Table 4. Independent Risk Factors for 30-Day Mortality after Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation.*

Risk Factor	Hazard Ratio (95% CI)	P Value
Antithrombotic medication at admission		
Neither aspirin nor warfarin	4.9 (1.8–13.7)	0.003
Aspirin	2.5 (0.9–7.4)	0.09
Warfarin, INR <2.0	3.4 (1.1–10.1)	0.03
Warfarin, INR ≥2.0†	1.0	—
Age (per decade)	2.2 (1.6–2.9)	<0.001
Heart failure	1.8 (1.2–2.7)	0.004
Coronary heart disease	1.1 (0.7–1.6)	0.67
Diabetes mellitus	2.1 (1.3–3.2)	<0.001
Hypertension	1.0 (0.7–1.6)	0.84
Prior ischemic stroke	1.0 (0.7–1.6)	0.84

* Estimates of effect were calculated with the use of Cox proportional-hazards models. All variables are dichotomous except for age. CI denotes confidence interval, and INR international normalized ratio.

† This group served as the reference group.

no antithrombotic medication. The outcome among patients who were taking aspirin when they had a stroke was similar to that among patients who were taking warfarin and whose admission INR was less than 2.0. The lessened severity of stroke associated with more intense anticoagulation may reflect a reduced proportion of strokes from a cardiac source, a smaller thrombus, or both.^{3,5,8}

Analyses relating the severity of stroke in patients with atrial fibrillation to the intensity of anticoagulation require large numbers of subjects who have a stroke while taking anticoagulants. Given the efficacy of anticoagulants for atrial fibrillation, it is difficult to find adequate numbers of subjects. In our cohort, there were 596 analyzable ischemic strokes, with 188 occurring among patients who were taking warfarin. By contrast, among five early primary-prevention trials of patients with atrial fibrillation there were only 27 strokes among patients treated with warfarin, and in the three Stroke Prevention in Atrial Fibrillation trials combined, there were only 25 strokes among those treated with adjusted-dose warfarin.^{8,16}

Our results have a direct bearing on the decisions regarding the use of anticoagulant therapy in patients with atrial fibrillation and the target INR level. Guidelines and formal decision analyses have focused exclusively on the efficacy of warfarin in preventing stroke in patients with atrial fibrillation.³⁰⁻³⁵ Our findings highlight an important incremental benefit of anticoagulation: strokes that occur among patients with adequate anticoagulation are far less likely to result in severe disability or death. In formal utility assessments, patients rate strokes very differently, depending on the severity of the resulting deficits. In particular, patients frequently rate severely disabling stroke as equivalent to or worse than death.³⁶ Recent guidelines of the American College of Cardiology–American Heart Association–European Society for Cardiology suggest the use of a lower INR target for certain patients with atrial fibrillation who are older than 75 years of age.³⁵ Our data indicate that an INR of less than 2.0 will substantially increase the likelihood of death and severe disability from atrial fibrillation–related stroke.^{18,37-42} We also observed little additional risk of intracranial hemorrhage with the use of warfarin until INR values exceeded 3.9. These findings weigh against the use of target INR values below 2.0.

Potential limitations of our study should be acknowledged. Ours was an observational assessment of the effect of treatment. Randomized trials of lower levels of anticoagulation would be difficult to implement, given prior negative results of such an approach, and the numbers of strokes would probably be too small for an assessment of the effect on the severity of stroke.^{18,19} We observed strong effects while simultaneously controlling for other important determinants of the outcome. Residual confounding by indication is particularly unlikely in our central comparison of two levels of anticoagulation, since both groups of patients were prescribed warfarin and had very similar INR values in the six months preceding their strokes.⁴³ It remains possible that some patients who had a minor stroke either did not seek medical care or were treated as outpatients. The 30-day mortality rate in the group of patients in our study who were not receiving anticoagulant therapy (24 percent) was similar to 30-day mortality rates for atrial fibrillation-related stroke in such population-based studies as the Framingham Study (25 percent),¹⁵ the Oxfordshire Community Stroke Project (23 percent),^{9,23} and the Italian Acute Stroke Study (27 percent),¹⁴ arguing against significant bias in our ascertainment of stroke. Furthermore, it is highly unlikely that the rates of hospitalization for minor strokes would be systematically disproportionate on the basis of the use or intensity of anticoagulation.

In this study of ischemic strokes in a large cohort of patients with nonvalvular atrial fibrillation, therapeutic anticoagulation resulting in an INR of 2.0 or greater at the time of the stroke was associated with less severe neurologic deficit than the absence of antithrombotic therapy or therapy that resulted in a lower INR. The 30-day mortality rate was 6 percent among patients who were taking warfarin and who had an INR of 2.0 or greater, as compared with 16 percent among those who were taking warfarin and who had an INR of less than 2.0,

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

INR	Person-yr†	Stroke (95% CI) (N=152)	Person-yr†	Intracranial Hemorrhage (95% CI) (N=58)
		rate/100 person-yr		rate/100 person-yr
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)
2.0–2.5	5357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (0.3–0.9)
3.1–3.5	834	0.7 (0.3–1.6)	843	0.6 (0.3–1.4)
3.6–3.9	243	0.4 (0.1–2.9)	247	0.4 (0.1–2.9)
4.0–4.5	144	1.4 (0.4–5.5)	147	2.7 (1.0–7.3)
>4.5	115	2.6 (0.8–8.1)	118	9.4 (5.2–16.9)

* CI denotes confidence interval.

† Differences in the numbers of person-years between stroke and intracranial hemorrhage reflect differences in the time at which data were censored.

15 percent among those who were taking aspirin, and 24 percent among those who were taking neither aspirin nor warfarin. There was no significant difference in mortality rates between patients taking warfarin who had an INR of 1.5 to 1.9 and those taking warfarin who had an INR of less than 1.5. The risk of intracranial hemorrhage in our cohort did not increase until INR values exceeded 3.9. Our results provide further support for the use of anticoagulation to achieve an INR of 2.0 or greater (e.g., 2.5) in patients with nonvalvular atrial fibrillation.

Supported by a grant from the National Institute on Aging (5 R01 AG15478).

Drs. Hylek and Singer report having received grant support from DuPont Pharma, now Bristol-Myers Squibb.

We are indebted to Dr. Philip A. Wolf of Boston University School of Medicine for providing expert consultation in neurology and epidemiology and to Kathleen A. Phillips and Angela M. Capra, M.A., of the Division of Research, Kaiser Permanente of Northern California, for providing technical assistance.

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