Racial/Ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients With Atrial Fibrillation

Albert Yuh-Jer Shen, Janis F. Yao, Somjot S. Brar, Michael B. Jorgensen, and Wansu Chen

J. Am. Coll. Cardiol. 2007;50;309-315; originally published online Jul 6, 2007;
doi:10.1016/j.jacc.2007.01.098

Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 4, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.098

Racial/Ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients With Atrial Fibrillation

Albert Yuh-Jer Shen, MS, MD, FACC,* Janis F. Yao, MS,† Somjot S. Brar, MD,* Michael B. Jorgensen, MD, FACC,* Wansu Chen, MS†

Los Angeles and Pasadena, California

Objectives This study was designed to study racial/ethnic differences in the risk for intracranial hemorrhage (ICH) and the effect of warfarin on ICH risk among patients with atrial fibrillation (AF).

Background Nonwhites are at greater risk for ICH than whites in the general population. Whether this applies to patients with AF and whether warfarin therapy is associated with comparable risk of ICH in nonwhites are unknown.

Methods We retrospectively identified a multiethnic stroke-free cohort hospitalized with nonrheumatic AF. Warfarin use and anticoagulation intensity were assessed by searching pharmacy and laboratory records. Crude ICH event rates were calculated by Poisson regression. Cox proportional hazard models were constructed to assess the independent effect of race/ethnicity on ICH after adjusting for age, gender, hypertension, diabetes, heart failure, and warfarin exposure.

Results Between 1995 and 2000, we identified 18,867 qualifying AF hospitalizations (78.5% white, 8% black, 9.5% Hispanic, and 3.9% Asian) and 173 qualifying ICH events over 3.3 years follow-up. Achieved anticoagulation intensity was lower among blacks but not different between the other groups. Warfarin was associated with increased ICH risk in all races, but the magnitude of risk was greater among nonwhites. There were no gender differences. The hazard ratio for ICH with whites as referent was 4.06 for Asians (95% confidence interval [CI] 2.47 to 6.65), 2.06 for Hispanics (95% CI 1.31 to 3.24), and 2.04 (95% CI 1.25 to 3.35) for blacks.

Conclusions Nonwhites with AF were at greater risk for warfarin-related ICH. Blacks, Hispanics, and Asians were at successively greater ICH risk than whites. (J Am Coll Cardiol 2007;50:309–15) © 2007 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is highly prevalent, is associated with a 5-fold increased risk of stroke (1), and may account for 10% to 15% of all strokes (2). In a pooled analysis of 5 primary stroke prevention trials, adjusted-dose warfarin reduced all strokes by 68% (4.5% vs. 1.4% per year) (2). This

See page 316

benefit was offset by a significant 0.3% increase in the annual risk of major bleeding (placebo 1.0%, warfarin 1.3%), the most severe of which was intracranial hemorrhage (ICH). The increase in ICH incidence is reported to be 0.2% per year (3,4). Go et al. (5) studied more than 11,000 nonvalvular AF patients in the Kaiser Permanente Northern California health plan and reported a 51% reduction in thromboembolic events with warfarin therapy but a doubling of ICH (0.46% vs. 0.23% per year).

Although most subjects in these studies were white, there are sparse data on whether the risks of anticoagulation among nonwhite patients parallel those of whites. Furthermore, there are demonstrated racial differences in the background incidence and types of stroke. The stroke incidences of Hispanics and blacks are more than twice as high as those of whites (6,7). Whereas ICH (intracerebral or subarachnoid hemorrhage) accounts for 15% to 20% of strokes in whites (8), it is substantially higher (20% to 30%) among blacks (9,10), Hispanics (6), and Asians (11,12). Death from ICH is also much more common among nonwhites (13).

Because of the higher baseline risk of ICH among nonwhites, it is important to assess whether there are racial/ethnic differences in AF-related stroke, particularly ICH, and whether nonwhite AF patients are at greater risk for ICH when treated with warfarin. This study's objective was to evaluate the risk of ICH among white, black, Hispanic, and Asian patients with a history of AF hospitalization.

From the *Department of Cardiology and the Center for Medical Education, and the †Department of Research and Evaluation, Kaiser Permanente Medical Center (KPMC), Pasadena, California.

Manuscript received November 7, 2006; revised manuscript received January 8, 2007, accepted January 17, 2007.

JACC Vol. 50, No. 4, 2007
July 24, 2007:309–15

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
DM = diabetes mellitus
HF = heart failure
ICD-9 = International Classification of Disease, 9th Revision, Clinical Modification
ICH = intracranial hemorrhage
INR = international normalized ratio

Methods

Kaiser Permanente Southern California (KPSC) is a prepaid health maintenance organization that has served at least 2.7 million members, about 14% of the region's population, for each of the past 10 years. Membership demographics and socioeconomic and racial/ethnic composition are representative of California. Racial/ethnic information is administratively assigned on all hospitalized patients. The study protocol was approved by our institutional review board.

Inclusion and exclusion criteria. By searching hospital discharge records, we identified all first-time hospitalizations for AF or atrial flutter between January 1, 1995, and December 31, 2000, among approximately 2.2 million adult KPSC members. Patients were identified by searching the first 3 discharge diagnoses for International Classification of Disease, 9th Revision, Clinical Modification (ICD-9) codes 427.31 and 427.32 for AF and atrial flutter, respectively. Any AF was included, whether permanent or intermittent, because the risk of stroke does not differ between these groups (14–16). Atrial flutter was included, as the risk for stroke even among "lone atrial flutter" parallels that of AF (17). By referencing ICD-9 and Current Procedural Terminology codes, patients with a history of stroke or transient ischemic attacks, rheumatic heart disease, mitral valvuloplasty, mitral valve replacement predating stroke/transient ischemic attack, brain tumor, heart transplantation, and congenital heart disease were excluded. Patients with prosthetic mitral valves were excluded because of their particularly high risk of thromboembolic events and higher target international normalized ratio (INR) levels (18).

Other risk factors for stroke listed by the National Registry of Atrial Fibrillation (19) were identified using appropriate ICD-9 codes, including heart failure (HF), hypertension, and diabetes mellitus (DM). Race/ethnicity was recorded in our administrative database for 95% of hospitalized patients. For this study, we grouped patients by race/ethnicity into 5 categories: white, black, Hispanic, Asian, or other. The 2.8% of patients identified as belonging to the "other" group were excluded from analysis.

Follow-up of each patient began on the day of AF admission and ended with an outcome event (fatal or nonfatal ICH) or censoring event (non-ICH stroke death, ischemic stroke, mitral valve replacement, carotid endarterectomy within 2 weeks of a stroke, disenrollment from health plan, and the end of study on December 31, 2003). Patients who underwent mitral valve replacement were censored, as they may have had a different stroke risk profile (18,20).

Stroke event identification. Ischemic strokes were identified by ICD-9 codes 433–436; ICHs were identified by codes 430–432. Data sources included hospital records and a computerized matching of Kaiser membership data with California vital statistics death tapes. Only the primary diagnosis from hospital files and the underlying cause of death from mortality files were used. All computer-identified ICHs underwent chart review to confirm that all patients underwent brain imaging and that ICH was primary and nontraumatic. Nonqualifying events were censored at the time of analysis.

Warfarin use and anticoagulation intensity. About 92% of Kaiser members have prescription drug benefits and obtain their drugs through a KPSC-owned pharmacy. Patients are typically dispensed a 100-day supply of medication, which may last longer because of splitting pills. All members have laboratory test benefits and typically have their prothrombin time tested at a Kaiser-owned laboratory with an INR target of 2 to 3 for uncomplicated AF.

We searched our pharmacy and laboratory databases to identify warfarin prescriptions and patients' achieved anticoagulation intensity. Patients with a filled warfarin prescription were considered to be continuously taking warfarin for the 100-day period after receiving the drug. For between-prescription gaps of 100 days or more, patients were considered to be continuously taking warfarin if they had an INR of 2 or greater in the intervening days. This was to account for pill-splitting and prescriptions filled at a non-Kaiser pharmacy. A therapeutic INR value was considered to be valid for up to 60 days if there were no subsequent INR values or if the warfarin supply was expected to have exhausted and there were no refills. Using this method, an individual patient may contribute to the follow-up times of both warfarin-treated and non–warfarin-treated groups. The proportion of follow-up time that patients were receiving warfarin according to this schema was designated "percent-time receiving warfarin."

Approximately 60% of patients received ≥1 warfarin prescription. We recorded all INR values that were performed while patients were taking warfarin according to the schema described. To exclude patients who were prescribed but may not have taken warfarin, we included for analysis only patients who had ≥3 INR values while taking warfarin. The INR tests performed during periods when the patients were not expected to have been taking warfarin according to their supply of warfarin were not included in our anticoagulation intensity analyses.

For all patients hospitalized with an ischemic stroke or ICH event, we reviewed their medical records to confirm whether or not they were taking warfarin, as well as the INR values at the time of admission. Comparison of patients' warfarin use status at the time of stroke defined by our computerized algorithm and that of our chart review showed a 90% consistency rate (kappa = 0.78).

Because warfarin-related stroke rates are associated with the achieved anticoagulation intensity, we analyzed the INR values over the follow-up period and at the time of ICH by race/ethnicity. The association between race/ethnicity and INR value at the time of stroke was studied using 3 different INR cut points (3.0, 3.5, and 4.0).

Statistical analysis. Continuous variables are reported as mean ± SD or median and interquartile range as appropriate. Continuous and categorical variables were compared among racial/ethnic groups with the Kruskal-Wallis test or chi-square test, respectively. Overall and risk factor-stratified crude event rates were calculated using log-linear (Poisson) regression with a generalized estimating equations approach and are reported as per 100 person-years of follow-up. Cox proportional hazard models were used to calculate the effect of race/ethnicity on the risk of stroke after adjusting for age, gender, hypertension, DM, HF, and percentage time receiving warfarin. Rate ratios and hazard ratios are reported with 95% confidence intervals (CI). Adjusted survival curves were constructed from the Cox model by setting the covariates at their means. All analyses were conducted with SAS software (version 9.1 for Windows, SAS Institute, Cary, North Carolina).

Results

Cohort characteristics. In the 6-year period that ended December 2000, we identified 22,196 first-time AF hospitalizations, of which 18,867 qualified for analysis (Table 1). The cohort median age was 74 years; nonwhites were about 6 years younger than whites. More than half of whites were older than 75 years, whereas only about a third of nonwhites were. A lesser proportion of Asians and Hispanics were women than among whites. Hypertension and HF were more prevalent among blacks. Whites were least likely to be diabetic. Hispanics and Asians had more stroke risk factors than the other 2 groups. About 40% to 45% of all patients were not prescribed warfarin at any time, whereas about 25% of patients took warfarin >80% of follow-up. There were no between-group differences.

Number of ICH events and follow-up person-years. Over the 9-year follow-up period, 185 ICH cases were identified. Ten were hemorrhagic conversions of index ischemic strokes, and 2 followed head trauma. By matching our AF cohort to California state death records for the entire study period, we found no cases of death due to ICH that were not captured into our database. There were thus 173 qualifying ICH events that occurred over 63,204

Table 1 Baseline Characteristics of Patients Hospitalized With Atrial Fibrillation by Race/Ethnicity

Characteristics	Race/Ethnicity					p Value
	White	Black	Hispanic	Asian	All	
n (%)	14,809 (78.5)	1,534 (8.1)	1,798 (9.5)	726 (3.9)	18,867	
Male, n (%)	8,353 (56.4)	830 (54.1)	1,079 (60.0)	468 (64.5)	10,730 (56.9)	<0.0001
Age (yrs)						
Mean ± SD	74 ± 11	68 ± 13	67 ± 14	68 ± 12	72 ± 12	<0.0001
Median (IQR)	75 (67–82)	70 (59–77)	69 (59–77)	69 (60–76)	74 (66–81)	<0.0001
Age in yrs, n (%)						
<55	885 (6.0)	240 (15.7)	327 (18.2)	114 (15.7)	1,566 (8.3)	<0.0001
55–64	1,814 (12.3)	326 (21.3)	335 (18.6)	158 (21.8)	2,633 (14.0)	
65–74	4,299 (29.0)	445 (29.0)	533 (29.6)	232 (32.0)	5,509 (29.2)	
75–84	5,572 (37.6)	396 (25.8)	440 (24.5)	170 (23.4)	6,578 (34.9)	
≥85	2,239 (15.1)	127 (8.3)	163 (9.1)	52 (7.2)	2,581 (13.7)	
Stroke risk factors, n (%)						
Hypertension	11,348 (76.6)	1,304 (85.0)	1,385 (77.0)	587 (80.9)	14,624 (77.5)	<0.0001
Diabetes mellitus	5,103 (34.5)	695 (45.3)	845 (47.0)	332 (45.7)	6,975 (37.0)	<0.0001
Heart failure	8,489 (57.3)	935 (61.0)	940 (52.3)	356 (49.0)	10,720 (56.8)	<0.0001
Number of stroke risk factors, n (%)*						
4	1,501 (10.1)	139 (9.0)	159 (8.8)	59 (8.1)	1,858 (9.9)	<0.0001
3	4,682 (31.6)	549 (35.8)	554 (30.8)	212 (29.2)	5,997 (31.8)	
2	4,946 (33.4)	489 (31.9)	560 (31.2)	229 (31.5)	6,224 (33.0)	
1	2,809 (19.0)	276 (18.0)	355 (19.7)	167 (23.0)	3,607 (19.1)	
0	871 (5.9)	81 (5.3)	170 (9.5)	59 (8.1)	1,181 (6.3)	
Follow-up in yrs, median (IQR)	3.2 (1.0–5.1)	3.1 (1.0–5.0)	3.4 (1.1–5.2)	3.7 (1.5–5.4)	3.3 (1.0–5.1)	<0.0001
Percent time receiving warfarin						
0%	6,132 (41.4)	695 (45.3)	737 (41.0)	287 (39.5)	7,851 (41.6)	0.067
1%–40%	2,823 (19.1)	270 (17.6)	341 (19.0)	157 (21.6)	3,591 (19.0)	
41%–80%	2,208 (14.9)	212 (13.8)	291 (16.2)	98 (13.5)	2,809 (14.9)	
81%–100%	3,646 (24.6)	357 (23.3)	429 (23.9)	184 (25.3)	4,616 (24.5)	

*Risk factors for stroke included age ≥75 years, hypertension, diabetes mellitus, and heart failure.
IQR = interquartile range.

JACC Vol. 50, No. 4, 2007
July 24, 2007:309–15

Table 2 Intracranial Hemorrhage Event Rates

	Receiving Warfarin	Not Receiving Warfarin	Rate Ratio (95% CI)
ICH events	114	59	
Total person-yrs	24,179	39,025	
Crude event rate/100 person-yrs (95% CI)	0.47 (0.27–0.83)	0.15 (0.12–0.20)	3.12 (2.28–4.27)
ICH/total person-yrs (rate)			
White	66/19,086 (0.34)	46/30,238 (0.15)	2.27 (1.56–3.31)
Black	14/1,807 (0.77)	5/3,197 (0.16)	4.95 (1.78–13.75)
Hispanic	17/2,313 (0.73)	6/3,892 (0.15)	4.77 (1.88–12.09)
Asian	17/971 (1.75)	2/1,698 (0.12)	14.86 (3.43–64.30)
Age (yrs)			
>75	49/8,529 (0.57)	38/16,343 (0.23)	2.47 (1.62–3.77)
<75	65/15,650 (0.42)	21/22,682 (0.09)	4.49 (2.74–7.34)
Gender			
Female	45/9,874 (0.46)	27/17,092 (0.16)	2.89 (1.79–4.65)
Male	69/14,304 (0.48)	32/21,933 (0.15)	3.31 (2.17–5.03)
Hypertension			
Yes	107/21,143 (0.51)	50/32,106 (0.16)	3.25 (2.32–4.55)
No	7/3,036 (0.23)	9/6,919 (0.13)	1.77 (0.66–4.76)
Diabetes mellitus			
Yes	46/10,321 (0.45)	23/14,817 (0.16)	2.87 (1.74–4.74)
No	68/13,858 (0.49)	36/24,207 (0.15)	3.30 (2.20–4.94)
Heart failure			
Yes	73/15,347 (0.48)	38/19,288 (0.20)	2.41 (1.63–3.57)
No	41/8,831 (0.46)	21/19,737 (0.11)	4.36 (2.58–7.38)
Stroke risk factors*			
≥1	113/23,157 (0.49)	58/36,018 (0.16)	3.03 (2.21–4.16)
0	1/1,021 (0.10)	1/3,006 (0.03)	2.94 (0.18–47.08)

*Risk factors for stroke include age ≥75 years, hypertension, diabetes, and heart failure.
CI = confidence interval; ICH = intracranial hemorrhage.

person-years of follow-up (0.27 ICH events/100 person-years). The numbers of ICH (total person-year follow-up) for each group are as follows: white 112 (49,324), black 19 (5,004), Hispanic 23 (6,206), and Asian 19 (2,669).

ICH event rate ratios while taking or not taking warfarin. As shown in Table 2, the crude rate of ICH for the entire cohort was 0.47 per 100 patient-years while taking warfarin and 0.15 while not taking warfarin, a rate ratio of 3.12. Although the risk of ICH increased with warfarin therapy in all groups, there were striking differences in the magnitude of increased risk. There was a 15-fold increased risk of ICH among Asians taking warfarin, whereas the rate ratios for Hispanics and blacks were 4.8 and 5.0, respectively. Warfarin-related ICH risk was lowest among whites at 2.3. As expected, the magnitude of risk was greater among older persons, but there were no gender differences in warfarin-related ICH in this cohort. Patients with hypertension had a 3.3-fold risk of ICH while taking warfarin. Those with 1 or more risk factors had a 3-fold risk for ICH, whereas there was only a single ICH event in each group among patients without risk factors. The ICH risk increased with warfarin whether or not DM or HF was present.

Adjusted hazard ratios. After adjusting for age, gender, hypertension, DM, HF, and percent time treated with warfarin, Hispanics and blacks had twice the risk for ICH as whites, whereas Asians were at 4 times the risk (Table 3, Fig. 1). There was a 4% increased risk of ICH with each advancing year in age. Patients with >41% time receiving warfarin had a 1.8- to 2.1-fold risk of ICH compared with those who were not treated with warfarin. Hypertension,

Table 3 Adjusted Hazard Ratio for Intracranial Hemorrhage

	Hazard Ratio	95% CI	p Value
Race			
White	1	—	
Black	2.05	1.25–3.36	0.005
Hispanic	2.06	1.31–3.24	0.002
Asian	4.06	2.48–6.66	<0.0001
Gender			
Male	1	—	
Female	0.86	0.63–1.17	0.33
Age (per yr)	1.04	1.03–1.06	<0.0001
Hypertension	1.52	0.90–2.57	0.12
Diabetes	0.90	0.66–1.23	0.50
Heart failure	1.14	0.82–1.57	0.43
Percent time receiving warfarin			
0%	1	—	
1%–40%	0.63	0.36–1.08	0.095
41%–80%	1.76	1.13–2.73	0.012
>80%	2.13	1.46–3.10	<0.0001

Abbreviations as in Table 2.

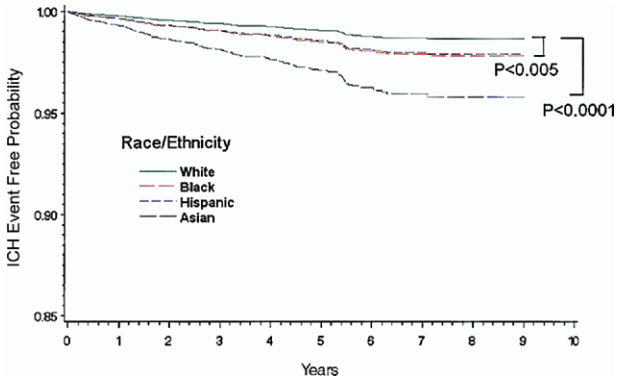

Figure 1 Adjusted ICH Event-Free Curve

ICH = intracranial hemorrhage.

DM, and HF were not independently associated with ICH in this cohort.

Achieved anticoagulation intensity. The median monthly number of INR values ranged from 2.51 in Asians to 2.67 in Hispanics ($p = 0.05$). The median duration of patient time that INR was ≥2 was approximately 70% in the entire cohort (Table 4). The patient time in subtherapeutic range (INR <2) was greater in blacks than in the others. Overall, 54.5% of patient-time was in the therapeutic range (INR 2 to 3), with blacks having a lower percentage of patient time in this range. Hispanics and Asians were in the therapeutic range for a similar percentage of follow-up time as whites. For approximately 9% of patient time, the INR values were >3, with no differences seen between groups.

INR at the time of ICH. The INR threshold value above which ICH and other major hemorrhagic risk increases varied between studies (21–23); therefore, INR values at the time of ICH hospitalization were analyzed using 3.0, 3.5, and 4.0 as cut points (Table 5). There was no statistically significant difference between groups in the proportion of ICH patients with INR >3.0 or ≥4.0, but minorities were more likely than whites to have an INR ≥3.5 at the time of ICH.

Discussion

The U.S. populace is becoming increasingly racially diverse. One in 4 residents is nonwhite, according to the 2000 Census. In some states (e.g., California), non-Hispanic whites constitute but half the population. However, literature on the epidemiology, prognosis, and treatment of nonwhites with AF are remarkably sparse. The Cardiovascular Health Study, which involved about 5,000 subjects, suggested that the incidence of AF in blacks was less than half that of whites, but only 5% of the total cohort was black (24). Data on nonblack minorities are even scarcer. In the Atrial Fibrillation Investigators pooled analysis (2), 90% were white. Even in the recent AFFIRM (Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management) study (15), which included 4,060 patients, only 11% were nonwhite.

Racial differences in ICH. There are important racial/ethnic differences in the incidence and mortality of ICH. In whites, ICH accounts for 15% to 20% of all strokes (6), whereas in Chinese (25), Japanese (26), and blacks (9), that percentage may be 1.5- to 2.0-fold higher. In the Northern Manhattan Stroke Study (6), with whites as referent, the age-adjusted relative risk of ICH was 2 to 3 for both Hispanics and blacks of either gender. Klatsky et al. (12) found that Northern California Asians had a 1.6-fold risk of ICH compared with whites. Furthermore, the Centers for Disease Control and Prevention reported a higher ICH mortality among Asians compared with whites (27). Among patients who died of stroke in the U.S. between 1995 and 1998, ICH accounted for 38% in Asians, 35% in Hispanics, 24% in blacks, and 18% among whites (13). These reports consistently indicate a higher baseline risk of ICH among minorities.

Risk factors for ICH. Advanced age, hypertension, and anticoagulation intensity are associated with a greater risk for warfarin-related bleeding, especially ICH (21,28). In our cohort, nonwhites were 6 to 7 years younger than whites, yet the adjusted hazard ratio for ICH was 2- to 4-fold than that of whites. There was a slightly higher proportion of hypertensives among Asians and blacks, but this does not appear sufficient to explain the excessive risk observed.

Achieved anticoagulation intensity. In this cohort, INR values were therapeutic more than half the time. Anticoagulation intensity was subtherapeutic more often among blacks than the other 3 groups, among which there were no differences. The observed excessive risk of ICH among nonwhites can therefore not be explained by over-anticoagulation.

Table 4 Percent Time Receiving Warfarin That INR Values Were ≥2, 2–3, and ≥3 by Race/Ethnicity

	Race/Ethnicity					
	White	Black	Hispanic	Asian	All	p Value
INR range, median (IQR)						
≥2	69.7 (50.6, 81.5)	63.2 (41.7, 76.7)	68.2 (50.9, 80.1)	69.5 (55.3, 81.1)	69.1 (50.3, 81.1)	<0.0001
2–3	55.2 (36.3, 67.8)	47.8 (27.0, 62.3)	54.0 (36.4, 66.9)	53.7 (39.1, 66.7)	54.5 (35.7, 67.4)	<0.0001
>3	9.1 (3.2, 16.2)	9.9 (2.5, 17.2)	9.1 (3.1, 16.8)	10.4 (3.9, 17.4)	9.2 (3.1, 16.4)	0.21

INR = international normalized ratio; IQR = interquartile range.

Table 5 Anticoagulation Intensity at the Time of Intracranial Hemorrhage by Race/Ethnicity

	Race/Ethnicity					
	White	Black	Hispanic	Asian	All	p Value
INR values, n (%)						
>3	24 (22.0)	5 (27.8)	9 (39.1)	6 (31.6)	44 (26.0)	0.32
≥3.5	12 (11.0)	5 (27.8)	6 (26.1)	6 (31.6)	29 (17.2)	0.03
≥4.0	10 (9.2)	3 (16.7)	3 (13.0)	3 (15.8)	19 (11.2)	0.57

INR = international normalized ratio.

Possible mechanisms. Polymorphisms of the P450 cytochrome CYP2C9, the enzyme responsible for metabolizing warfarin, partially determine the dose required. Several studies have suggested racial differences in population frequencies of certain polymorphisms (29) that result in a higher risk of warfarin-related serious bleed (30). However, other studies have suggested that CYP2C9 polymorphisms do not fully account for the population differences in warfarin dose requirement (29). Variants in the gene for vitamin K epoxide reductase complex 1 (VKORC1), the target enzyme of warfarin, also affect patients' response to warfarin (31,32). Recent studies (33,34) have found that the frequency of the haplotypes predictive of a low warfarin dose was significantly higher in the Asian-American population (~89%) and lower in the African-American population (10% to 14%) than in the European-American population (37% to 42%). Whether this influenced our observation of higher ICH risks among nonwhites is not known.

Clinical implications. Because dosing studies of warfarin have involved mostly whites, physicians likely dose warfarin for patients of all races either empirically or based on nomograms derived from predominantly white patients (35). However, several studies have shown that to achieve the same INR range, Asians require lower warfarin doses, whites require intermediate doses, and blacks require higher doses (36,37). It is unknown whether nonwhites in this cohort had greater fluctuation in INR levels and whether this influenced the different rates of ICH observed.

An important consideration is whether all races/ethnicities require the same anticoagulation intensity. You et al. (38) suggested that a target INR of 1.8 to 2.4 is associated with less thromboembolic and hemorrhagic events than INRs of 2 to 3 for Chinese patients. There are few studies addressing racial differences in the optimal INR range. It is important for future studies to assess whether anticoagulation intensity should be modified based on race.

Study limitations. This cohort consists of patients who had been hospitalized with AF as one of the primary diagnoses. One study suggested that as few as 30% of AF patients are ever hospitalized (39). Our results may not apply to patients who were never hospitalized. ICD-9 codes were used for all disease identification in this study. A recent study (40) showed that ICD-9 coding for AF and other stroke risk factors was >80% sensitive and specific. Although ICD-9 codes may not capture all morbidities, they have excellent negative predictive value (0.98) and moderate positive predictive value for ICH (0.54 to 0.77) (41). This limitation was addressed by manual confirmation of all ICH.

In this study, hypertension was considered a dichotomous risk factor (present/absent). We could not adjust for the stage of hypertension or the adequacy of blood pressure control. Nor could we control for other factors known to affect the risk of ICH (e.g., alcohol or illicit drug use) or drugs that interact with warfarin (e.g., acetaminophen or herbs), which use may be heterogeneous among racial groups. Despite our use of both pharmacy and laboratory values, we cannot ascertain the day-to-day fluctuation of anticoagulation intensity and whether this influenced the rates of ICH. Finally, racial/ethnic classification was administratively assigned rather than self-reported. Our administrative database did not differentiate between East and South Asians, but regional demographics indicate that East Asians predominate.

Conclusions

In this multiethnic cohort of patients hospitalized with AF, all races experienced increased risk of ICH while taking warfarin. However, nonwhite patients, especially Asians, experienced substantially higher risk for warfarin-related ICH compared with whites. Furthermore, the adjusted hazard ratio for nonwhites was 2- to 4-fold that of whites.

Reprint requests and correspondence: Dr. Albert Yuh-Jer Shen, Department of Cardiology, 1526 Edgemont Street, 2nd Floor, Kaiser Foundation Hospitals, Los Angeles, California 90027. E-mail: albert.y-j.shen@kp.org.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
2. Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. Arch Intern Med 1994;154:1449–57.
3. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs. aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002;288:2441–8.
4. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:287S–310S.

5. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685–92.
6. Sacco RL, Boden-Albala B, Gan R, et al. Stroke incidence among white, black, and Hispanic residents of an urban community: the Northern Manhattan Stroke Study. Am J Epidemiol 1998;147:259–68.
7. Pandey DK, Gorelick PB. Epidemiology of stroke in African Americans and Hispanic Americans. Med Clin North Am 2005;89:739–52.
8. Thrift AG, Dewey HM, Macdonell RA, McNeil JJ, Donnan GA. Incidence of the major stroke subtypes: initial findings from the North East Melbourne stroke incidence study (NEMESIS). Stroke 2001;32:1732–8.
9. Broderick JP, Brott T, Tomsick T, Huster G, Miller R. The risk of subarachnoid and intracerebral hemorrhages in blacks as compared with whites. N Engl J Med 1992;326:733–6.
10. Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. Neurology 2005;65:518–22.
11. Hu HH, Sheng WY, Chu FL, Lan CF, Chiang BN. Incidence of stroke in Taiwan. Stroke 1992;23:1237–41.
12. Klatsky AL, Friedman GD, Sidney S, Kipp H, Kubo A, Armstrong MA. Risk of hemorrhagic stroke in Asian American ethnic groups. Neuroepidemiology 2005;25:26–31.
13. Ayala C, Croft JB, Greenlund KJ, et al. Sex differences in US mortality rates for stroke and stroke subtypes by race/ethnicity and age, 1995–1998. Stroke 2002;33:1197–201.
14. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol 2000;35:183–7.
15. Sherman DG, Kim SG, Boop BS, et al. Occurrence and characteristics of stroke events in the Atrial Fibrillation Follow-up Investigation of Sinus Rhythm Management (AFFIRM) study. Arch Intern Med 2005;165:1185–91.
16. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 2006;48:e149–246.
17. Halligan SC, Gersh BJ, Brown RD Jr., et al. The natural history of lone atrial flutter. Ann Intern Med 2004;140:265–8.
18. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease—native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:457S–82S.
19. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.
20. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briet E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med 1995;333:11–7.
21. Fang MC, Chang Y, Hylek EM, et al. Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. Ann Intern Med 2004;141:745–52.
22. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med 2004;164:880–4.
23. The European Atrial Fibrillation Trial Study Group. Optimal oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and recent cerebral ischemia. N Engl J Med 1995;333:5–10.
24. Psaty BM, Manolio TA, Kuller LH, et al. Incidence of and risk factors for atrial fibrillation in older adults. Circulation 1997;96:2455–61.
25. Fang J, Foo SH, Jeng JS, Yip PK, Alderman MH. Clinical characteristics of stroke among Chinese in New York City. Ethn Dis 2004;14:378–83.
26. Tanaka H, Ueda Y, Hayashi M, et al. Risk factors for cerebral hemorrhage and cerebral infarction in a Japanese rural community. Stroke 1982;13:62–73.
27. Ayala C, Greenlund KJ, Croft JB, et al. Racial/ethnic disparities in mortality by stroke subtype in the United States, 1995–1998. Am J Epidemiol 2001;154:1057–63.
28. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897–902.
29. Takahashi H, Wilkinson GR, Caraco Y, et al. Population differences in S-warfarin metabolism between CYP2C9 genotype-matched Caucasian and Japanese patients. Clin Pharmacol Ther 2003;73:253–63.
30. Aithal GP, Day CP, Kesteven PJ, Daly AK. Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. Lancet 1999;353:717–9.
31. Quteineh L, Verstuyft C, Descot C, et al. Vitamin K epoxide reductase (VKORC1) genetic polymorphism is associated to oral anticoagulant overdose. Thromb Haemost 2005;94:690–1.
32. Rost S, Fregin A, Ivaskevicius V, et al. Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature 2004;427:537–41.
33. Takahashi H, Wilkinson GR, Nutescu EA, et al. Different contributions of polymorphisms in VKORC1 and CYP2C9 to intra- and inter-population differences in maintenance dose of warfarin in Japanese, Caucasians and African-Americans. Pharmacogenet Genomics 2006;16:101–10.
34. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005;352:2285–93.
35. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:204S–233S.
36. Dang M-TN, Hambleton J, Kayser SR. The influence of ethnicity on warfarin dosage requirement. Ann Pharmacother 2005;39:1008–12.
37. Yu HC, Chan TY, Critchley JA, Woo KS. Factors determining the maintenance dose of warfarin in Chinese patients. Q J Med 1996;89:127–35.
38. You JH, Chan FW, Wong RS, Cheng G. Is INR between 2.0 and 3.0 the optimal level for Chinese patients on warfarin therapy for moderate-intensity anticoagulation? Br J Clin Pharmacol 2005;59:582–7.
39. Lip GY, Golding DJ, Nazir M, Beevers DG, Child DL, Fletcher RI. A survey of atrial fibrillation in general practice: the West Birmingham Atrial Fibrillation Project. Br J Gen Pract 1997;47:285–9.
40. Kokotailo RA, Hill MD. Coding of stroke and stroke risk factors using international classification of diseases, revisions 9 and 10. Stroke 2005;36:1776–81.
41. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–5.

Racial/Ethnic Differences in the Risk of Intracranial Hemorrhage Among Patients With Atrial Fibrillation

Albert Yuh-Jer Shen, Janis F. Yao, Somjot S. Brar, Michael B. Jorgensen, and Wansu Chen

J. Am. Coll. Cardiol. 2007;50;309-315; originally published online Jul 6, 2007;
doi:10.1016/j.jacc.2007.01.098