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ORIGINAL RESEARCH

Incident Strokes Among American Indian Individuals With Atrial Fibrillation

José M. Sanchez, MD; Stacey E. Jolly, MD, MAS; Thomas A. Dewland, MD; Zian H. Tseng, MD, MAS; Gregory Nah, MA; Eric Vittinghoff, PhD, MPH; Gregory M. Marcus, MD, MAS

BACKGROUND: American Indian individuals experience a relatively high risk for cardiovascular disease and have exhibited a higher risk of stroke compared with other racial and ethnic minorities. Although this population has the highest incidence of atrial fibrillation (AF) compared with other groups, the relationship between AF and nonhemorrhagic stroke among American Indian individuals compared with other groups has not been thoroughly studied.

METHODS AND RESULTS: We used the Healthcare Cost and Utilization Project to evaluate risk of nonhemorrhagic stroke among American Indian individuals, with comparisons to White, Black, Hispanic, and Asian individuals, among all adult California residents receiving care in an emergency department, inpatient hospital unit, or ambulatory surgery setting from 2005 to 2011. Of 16 951 579 patients followed for a median 4.1 years, 105 822 (0.6%) were American Indian. After adjusting for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cardiac surgery, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use, American Indian individuals with AF exhibited the highest risk of nonhemorrhagic stroke when compared with either non-American Indian individuals with AF (hazard ratio, 1.38; 95% CI, 1.23–1.55; $P<0.0001$) or to each race and ethnicity with AF. American Indian individuals also experienced the highest overall risk for stroke, with no evidence that AF disproportionately heightened that risk in interaction analyses.

CONCLUSIONS: American Indian individuals experienced the highest risk of nonhemorrhagic stroke, whether in the presence or absence of AF. Our findings likely suggest an opportunity to further study, if not immediately address, guideline-adherent anticoagulation prescribing patterns among American Indian individuals with AF.

Key Words: atrial fibrillation ■ race and ethnicity ■ stroke

Stroke is the second leading cause of cardiovascular-related death and serious long-term disability in the United States.[1,2] Across multiple studies, racial and ethnic minority groups have consistently exhibited the highest incidence of stroke compared with White individuals.[3–6] Atrial fibrillation (AF) is a potent risk factor for stroke, and, despite a lower prevalence of AF among some minority groups,[1,7–10] those same populations often experience a higher risk for stroke once AF is present.[4,11–13] Understanding the relationship between AF and stroke in particular populations is important for several reasons: first, given an AF diagnosis, the great majority of strokes can be prevented with appropriate guideline-based anticoagulation prescription.[14,15] Second, stroke is a readily identifiable marker of AF-associated thromboembolic risk, likely indicative of AF-related risks of myocardial infarction,[16] chronic kidney disease,[17] and dementia.[18]

We recently demonstrated that American Indian individuals exhibit the highest risk of AF compared with other racial or ethnic groups.[10] Although American Indian individuals are known to carry a particularly high risk for stroke in general,[6,19] the relationship between AF and nonhemorrhagic stroke

Correspondence to: Gregory M. Marcus, MD, MAS, 505 Parnassus Ave, M1180B, San Francisco, CA 94143-0124, USA. E-mail: greg.marcus@ucsf.edu
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CLINICAL PERSPECTIVE

What Is New?

- American Indian individuals experience the highest risk of stroke when compared with other racial and ethnic groups, whether in the presence or absence of atrial fibrillation, and despite multivariable adjustment.

What Are the Clinical Implications?

- Our study highlights the significant health risks accrued by American Indian individuals and their vulnerability to stroke and suggests that unaccounted-for factors are driving these observations.
- This may help guide community efforts aimed at cardiovascular risk factor prevention.

Nonstandard Abbreviations and Acronyms

HCUP Healthcare Cost and Utilization Project

among American Indian individuals has not been thoroughly studied.

METHODS

All patients aged ≥18 years who received care in a California emergency department, inpatient hospital unit, or ambulatory surgery setting between January 1, 2005 and December 31, 2011 were identified using Healthcare Cost and Utilization Project (HCUP, Agency for Healthcare Research and Quality) California State Emergency Department Databases, State Inpatient Databases, and State Ambulatory Surgery Databases. Individual databases specific to calendar year and healthcare setting were merged using an encrypted linkage variable to identify repeat visits for a given patient. Patients with missing admission date data, residence outside of the state of California, unknown race or ethnicity, or a race or ethnicity other than American Indian, White, Black, Hispanic, or Asian were excluded. Patients with prevalent stroke (defined as stroke at the first recorded hospital encounter) were also excluded from incident analyses. Individuals entered the study cohort at their first healthcare encounter and were censored upon the diagnosis of stroke or at the time of inpatient death. Patients who did not experience either of these outcomes were administratively censored at the end of the study period (December 31, 2011). The data belong to HCUP, and the authors therefore do not have the authority to share the study data with investigators outside the University of California, San Francisco; however, investigators can submit an application to obtain the data directly from HCUP using their established processes.

Age, sex, race, income level, and insurance payer were recorded at each healthcare encounter by the discharging institution. Race and Hispanic ethnicity are reported separately in HCUP data, and Hispanic was analyzed as a mutually exclusive category if either White or "other" race was selected. American Indian was defined by sole selection of the American Indian race. Income level was categorized by quartiles using the median household income for the patient's ZIP code. Up to 25 *International Classification of Diseases, Ninth Edition* (*ICD-9*) codes and 21 Current Procedural Terminology codes were provided for each encounter. Stroke was defined using the *ICD-9* codes for nonhemorrhagic stroke: 434.01, 434.11, and 434.91. The association between race and incident nonhemorrhagic stroke was examined, including comparisons among those with and without a diagnosis of AF occurring either before or during the same encounter. Medical comorbidities postulated to confound or mediate the association between race and stroke were recorded using *ICD-9* and Current Procedural Terminology codes as previously described (Table S1).[7,20] Because postoperative stroke may have a different underlying mechanism than stroke occurring outside of the acute surgical setting, stroke was not recorded if a patient had undergone cardiothoracic surgery during the same hospitalization or within the previous 30 days. Dichotomous medical comorbidity variables were accumulated at each healthcare encounter and carried forward over time. We also performed interaction testing to determine if AF was a statistically significant effect modifier of the relationship between race, ethnicity, and nonhemorrhagic stroke.

To address the possibility that our observations were driven by a differential representation of race by varying levels of patient acuity or by frequency of healthcare encounters, we performed 2 sensitivity analyses. First, we repeated our analyses after excluding all outpatient surgery encounters. Second, we repeated the analyses excluding those under age 35 as well as those with only 1 encounter.

Statistical Analysis

Continuous variables with a normal distribution are presented as means± SD and were compared using *t* tests. Nonnormally distributed continuous variables are presented as medians with interquartile ranges and were compared using the Kruskal-Wallis test. The association between categorical variables was determined using χ^2 tests. Kaplan-Meier analysis was used to estimate the incidence of nonhemorrhagic stroke. Adjusted person-time incidence rates by race and ethnicity for incident stroke were estimated and compared using Poisson models with log follow-up time as an offset. Cox proportional hazards models were used to investigate the association both before and after adjusting for potential mediators and confounders. In these models, insurance payer, income level, and medical comorbidities were treated as time-dependent covariates. Proportional hazard assumptions were tested and confirmed using log-log survival plots, comparison of Kaplan-Meier and predicted survival plots, and test for the correlation of scaled Schoenfeld residuals with time. Interaction testing, with the outcome of stroke, was performed with the fully adjusted Cox model absent the candidate effect modifier of interest.

Analyses were performed using Stata version 15 (StataCorp) and SAS 9.4 (SAS Institute Inc.). A 2-tailed $P<0.05$ was considered statistically significant. The HCUP research protocol was approved by its institutional review board, and all participants provided written informed consent. Certification to use deidentified HCUP data was obtained from the University of California, San Francisco Committee on Human Research and the institutional review board. In accord with regulations governing use of HCUP data, no details for cells of <10 patients are reported.

RESULTS

After incorporating exclusion criteria, 16 951 579 patients were available for analysis (Figure S1). Of these, 105 822 (0.6%) were American Indian, 9 618 043 (56.7%) were non-Hispanic White, 1 367 992 (8.1%) were Black, 4 395 503 (25.9%) were Hispanic, and 1 464 219 (8.7%)

Table 1. Baseline Characteristics by Race

	American Indian (n=105 822)	White (n=9 618 043)	Black (n=1 367 992)	Hispanic (n=4 395 503)	Asian (n=1 464 219)	*P* Value
Mean age, y	45.5±17.8	50.5±19.3	43.6±17.8	41.9±17.7	49.7±18.7	<0.0001
Female, n (%)	58 642 (55.4)	5 013 667 (52.1)	735 066 (53.7)	2 388 853 (54.3)	876 569 (59.9)	<0.0001
Hypertension, n (%)	17 570 (16.6)	1 691 221 (17.6)	289 000 (21.1)	625 536 (14.2)	305 597 (20.9)	<0.0001
Diabetes mellitus, n (%)	12 307 (11.6)	686 852 (7.1)	132 065 (9.7)	441 171 (10.0)	158 617 (10.8)	<0.0001
Coronary artery disease, n (%)	3873 (3.7)	435 393 (4.5)	40 475 (2.9)	107 058 (2.4)	62 073 (4.2)	<0.0001
Heart failure, n (%)	1765 (1.7)	170 778 (1.8)	32 682 (2.4)	49 522 (1.1)	22 567 (1.5)	<0.0001
Cardiothoracic surgery, n (%)	631 (0.6)	45 990 (0.5)	7527 (0.5)	18 279 (0.4)	5825 (0.4)	<0.0001
Valvular disease, n (%)	710 (0.7)	106 242 (1.1)	7945 (0.6)	18 660 (0.4)	11 449 (0.8)	<0.0001
Smoking, n (%)	6764 (6.4)	533 216 (5.5)	91 198 (6.7)	144 936 (3.3)	37 758 (2.6)	<0.0001
Obstructive sleep apnea, n (%)	847 (0.8)	97 040 (1.0)	10 873 (0.8)	23 405 (0.5)	6959 (0.5)	<0.0001
Pulmonary disease, n (%)	1399 (1.3)	181 749 (1.9)	16 972 (1.2)	25 543 (0.6)	14 084 (1.0)	<0.0001
Chronic kidney disease, n (%)	1951 (1.8)	140 099 (1.5)	35 858 (2.6)	61 144 (1.4)	34 065 (2.3)	<0.0001
Obesity, n (%)	4105 (3.9)	322 316 (3.4)	57 046 (4.2)	154 964 (3.5)	20 908 (1.4)	<0.0001
Alcohol use, n (%)	1578 (1.5)	92 483 (1.0)	9730 (0.7)	32 130 (0.7)	3072 (0.2)	<0.0001
Insurance, n (%)						
Medicare	21 435 (20.2)	2 493 338 (25.9)	201 435 (14.7)	544 139 (12.4)	293 244 (20.0)	<0.0001
Medicaid	19 650 (18.6)	609 796 (6.3)	241 131 (17.6)	915 212 (20.9)	143 682 (9.8)	
Private	36 377 (34.4)	5 021 253 (52.3)	533 829 (39.1)	1 824 659 (41.5)	839 904 (57.4)	
Self-pay	18 484 (17.5)	911 101 (9.5)	277 761 (20.3)	744 512 (16.9)	99 001 (6.8)	
Other	9876 (9.3)	582 555 (6.0)	113 836 (8.3)	366 981 (8.3)	88 388 (6.0)	
Income quartile, n (%)						
1 Lowest	36 454 (34.5)	1 638 257 (17.0)	596 600 (43.6)	1 542 393 (35.1)	211 019 (14.4)	<0.0001
2	29 927 (28.3)	2 149 633 (22.4)	325 238 (23.8)	1 413 693 (32.2)	269 149 (18.4)	
3	23 848 (22.5)	2 731 022 (28.4)	298 318 (21.8)	944 348 (21.5)	475 811 (32.5)	
4 Highest	15 593 (14.7)	3 099 131 (32.1)	147 836 (10.8)	495 069 (11.2)	508 240 (34.7)	
First encounter location, n (%)						
Ambulatory surgery	19 674 (18.6)	2 445 219 (25.4)	135 517 (9.9)	656 519 (14.9)	352 800 (24.1)	<0.0001
Emergency department	62 729 (59.3)	4 803 586 (49.9)	889 054 (65.0)	2 748 961 (62.5)	703 294 (48.0)	
Inpatient hospitalization	23 419 (22.1)	2 369 238 (24.7)	343 421 (25.1)	990 023 (22.6)	408 125 (27.9)	

were Asian. American Indian individuals had a lower prevalence of private health insurance, exhibited lower incomes, and frequently carried diagnoses of diabetes mellitus, obesity, and smoking (Table 1).

There were 166 826 incident nonhemorrhagic strokes over a median follow-up of 4.1 years (interquartile range, 2.5–5.3), of which 36 950 occurred in patients with AF. American Indian individuals as a group experienced the highest rates of nonhemorrhagic stroke whether compared with all other racial and ethnic groups combined or to each individual racial and ethnic group (Table 2). Similarly, American Indian individuals with AF exhibited higher rates of nonhemorrhagic stroke compared with all other racial and ethnic groups with AF, either combined or in individual-group comparisons (Table 2). After adjusting for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cardiac surgery, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use, American Indian individuals as a group exhibited a 47% higher risk of nonhemorrhagic stroke than the rest of the cohort (hazard ratio [HR] 1.47; 95% CI, 1.40–1.55; *P*<0.0001), and American Indian individuals with AF exhibited a nearly 40% higher risk of nonhemorrhagic stroke compared with non-American Indian individuals with AF (HR, 1.38; 95% CI, 1.23–1.55; *P*<0.0001; Figure 1). Similar results were obtained in sensitivity analyses when restricted to individuals with encounters in only emergency departments or inpatient hospital units, and in individuals of age >35 years with at least 2 encounters (Figure S2). After adjusting for the same covariates, the risk of nonhemorrhagic stroke in American Indian individuals with AF was significantly higher compared with each racial and ethnic group with AF (Figure 2). Interaction analyses failed to demonstrate that AF accentuated the increased risk for nonhemorrhagic stroke among American Indian individuals: an approximate 60% increased risk for American Indian individuals without AF (HR, 1.59; 95% CI, 1.51–1.67) and approximate 40% increased risk for American Indian individuals with AF (HR, 1.39; 95% CI, 1.24–1.57, *P* for interaction = 0.05).

Table 2. Adjusted Incident Rates of Stroke

	Adjusted Incident Rates per 1000 patient years (95% CI)	*P* Value
Overall strokes	2.70 (2.68–2.71)	
American Indian	3.30 (3.15–3.47)	<0.0001*
Non-American Indian	2.69 (2.68–2.70)	
White	2.84 (2.83–2.86)	<0.0001†
Black	3.05 (3.00–3.10)	<0.0001†
Hispanic	2.04 (2.02–2.06)	<0.0001†
Asian	2.87 (2.82–2.91)	<0.0001†
Strokes among atrial fibrillation patients	17.6 (17.4–17.8)	
American Indian	21.8 (19.3–24.4)	<0.0001*
Non-American Indian	17.6 (17.4–17.7)	
White	16.6 (16.4–16.8)	<0.0001†
Black	20.1 (19.7–20.5)	<0.0001†
Hispanic	19.9 (19.4–20.4)	<0.0001†
Asian	19.2 (18.5–19.9)	<0.0001†

Incident rates are adjusted for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cardiac surgery, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use.

**P* value for comparison of American Indian vs non-American Indian individuals.

†*P* value for comparison of American Indian individuals vs each individual race/ethnicity.

DISCUSSION

American Indian individuals experienced the highest risk of nonhemorrhagic stroke, whether assessed among different racial and ethnic groups and whether in the presence or absence of AF. A persistently elevated risk after adjusting for conventional risk factors, including several that could mediate these relationships such as hypertension and diabetes mellitus, suggests that unknown or unaccounted for factors are driving these observations and warrant further attention.

The results of our study add to the growing body of data that race and ethnicity are important factors in determining stroke risk, now highlighting the vulnerability of American Indian individuals to this severe outcome in both the presence and absence of AF. Initially, Black individuals were shown to have a higher risk of stroke and more disabling strokes than White individuals.[3,21–23] Subsequently, Hispanic individuals were found to have a high incidence of stroke, with particularly strong evidence of this higher risk specifically among Mexican American individuals.[4,5,12] In populations with AF, the risk of stroke mirrors a similar pattern, where Black individuals have the highest risk followed by Hispanic and then White individuals.[11,13]

The relationship between race, ethnicity, and AF-related stroke may play an important role in clinical practice. For example, inclusion of the Black race to the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65 to 74 years, sex category (CHA_2DS_2-VASc) scoring system has been shown to significantly improve the prediction of stroke events among newly diagnosed AF patients.[13] Because thromboembolic stroke in AF is preventable using appropriate anticoagulation therapy, evidence

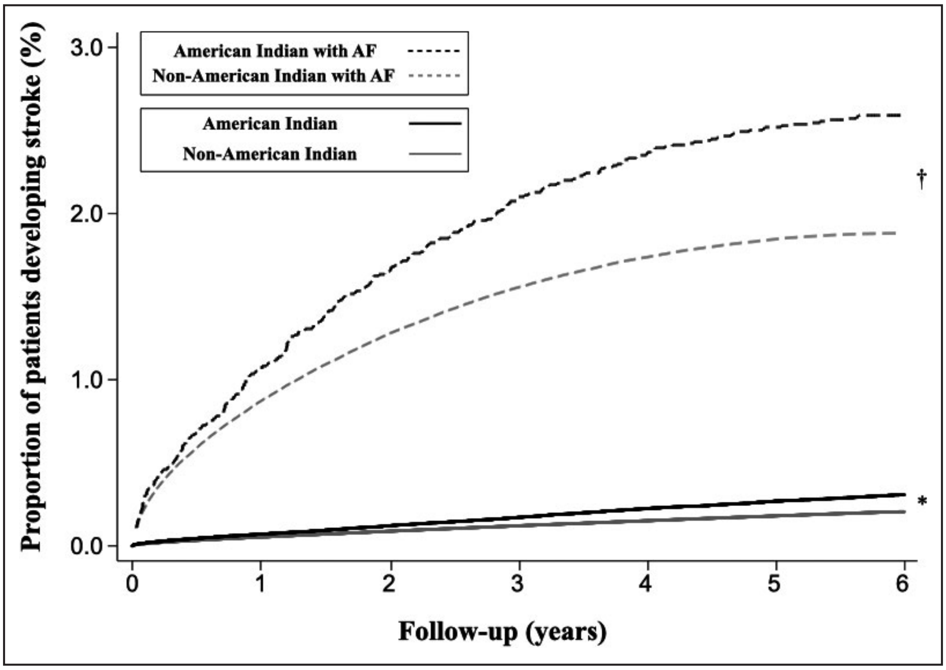

Figure 1. Adjusted Kaplan-Meier curves for incident nonhemorrhagic stroke in American Indian and non-American Indian patients with and without AF.

The curves are adjusted for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, cardiac surgery, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use. AF indicates atrial fibrillation. *Comparison between American Indian to non-American Indian individuals, *P* value<0.0001. †Comparison between American Indian individuals with AF to non-American Indian individuals with AF, *P* value<0.0001.

of heightened AF-related stroke in certain populations may point to opportunities for quality improvement in guideline adherence that could translate into meaningful improvements in care. In addition, AF-related stroke in a given population may be considered the "tip of the iceberg," as other thromboembolic complications less readily attributed to AF, such as myocardial infarction,[16] progressive chronic kidney disease,[17] dementia,[18] and perhaps other manifestations of acute or chronic showering of thromboemboli are now recognized as complications of AF that may be mitigated by appropriate anticoagulation.[24,25]

Among American Indian individuals, cardiovascular disease is the leading cause of death, with particularly high rates of hypertension, diabetes mellitus, smoking, and coronary heart disease.[19,26–29] Furthermore, we recently demonstrated that American Indian individuals exhibit the highest risk of AF when compared with White, Black, Hispanic, and Asian individuals.[10] Observational studies also have demonstrated a high incidence of stroke in American Indian individuals compared with White, Black, and Hispanic individuals, but the relative influence of AF has not previously been analyzed.[5,6,19,30,31]

To our knowledge, only 1 previous study has reported the relationship between American Indian individuals and stroke in comparison to other racial and ethnic minorities with AF.[13] In that study, the authors reported that Black individuals have the highest rate of AF-related stroke followed by American Indian, Hispanic, White, and then Asian individuals. Although that study was thorough and longitudinal in design, the population was limited to those over the age of 65 years and with a mean follow-up of 18 months, and interactions related to the presence versus absence of AF were not examined. Interestingly, a subsequent study limited to Black and Hispanic individuals with AF demonstrated that the elevated stroke risk persisted despite adjustment for anticoagulation status.[11] Regardless, as anticoagulation has proven to be such an effective approach to mitigating stroke and thromboembolic risk in AF,[32,33] our findings likely suggest an opportunity to further study, if not immediately address, guideline-adherent anticoagulation prescribing patterns among American Indian individuals with AF.

There are several possible explanations for our observations. A differential impact of stroke risk factors across racial and ethnic groups has been proposed.[34] Although the current data set allows us to capture those diagnoses, we were unable to assess severity or control of those comorbidities. Indeed, poor control of hypertension, diabetes mellitus, and congestive heart

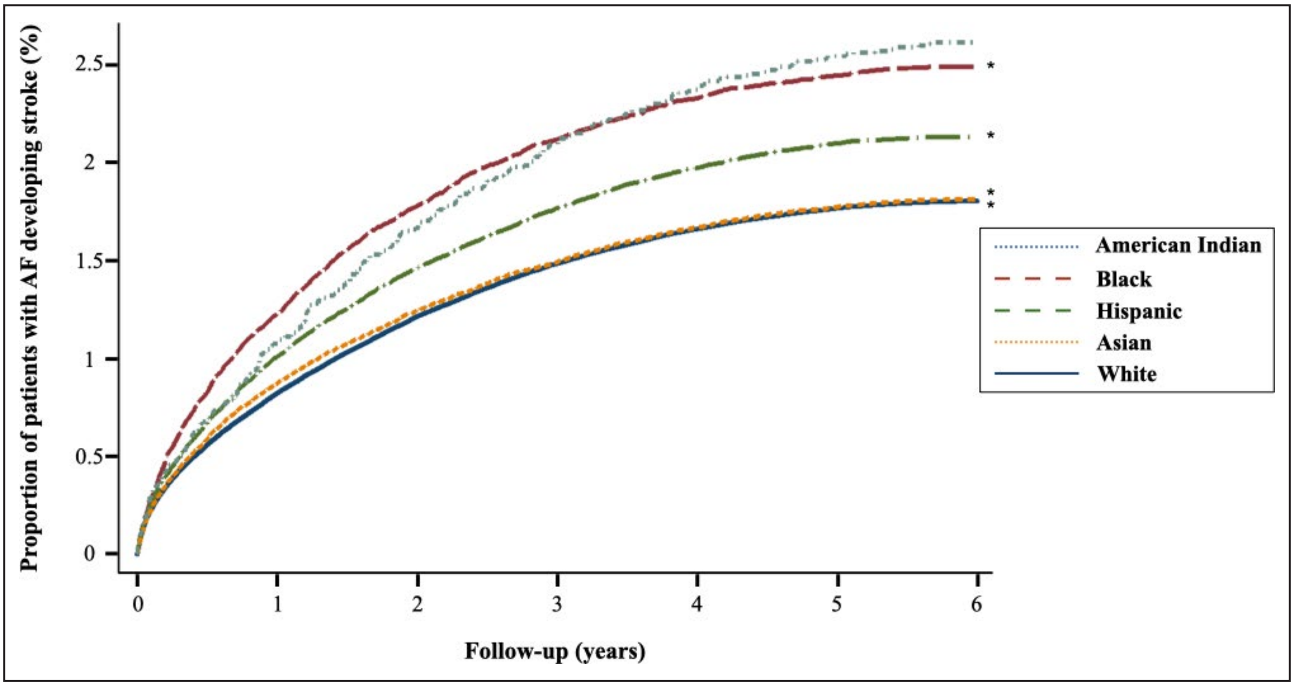

Figure 2. Adjusted Kaplan-Meier curves for incident stroke in American Indian, White, Black, Hispanic, and Asian patients with atrial fibrillation.

The curves are adjusted for age, sex, income level, insurance payer, hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use. *Comparison between American Indian individuals to each individual race and ethnicity, *P* value<0.0001. AF indicates atrial fibrillation.

failure is often more common among minority populations,[35–37] which may augment nontraditional risk factors or result in a heightened degree of systemic inflammation leading to an increased risk of stroke.[38–41] Our finding that AF did not accentuate incident stroke risk is important and may be attributed to the young age of American Indian individuals in our study population (mean age of 45.5 years) that statistical adjustment did not adequately address. The effect of AF on stroke risk has been shown to be highly dependent on age.[8] For example, AF is the only independent stroke risk factor in those aged over 80 years, whereas other stroke risk factors carry more weight in younger populations.[8]

Equally important to our findings are the healthcare disparities experienced by American Indian individuals. Limited funding of American Indian healthcare delivery systems and overall access to care among those living in urban areas are perpetual problems.[42] American Indian individuals have among the highest rates of obesity, diabetes mellitus, and cardiovascular disease, likely rooted in the lower health status that is experienced compared with other American individuals.[19,43] This translates into a lower life expectancy among American Indian individuals that is 5.5 years less than non-American Indian individuals in the United States.[44] Our study results are critical in understanding the significant health risks accrued by American Indian individuals and may help guide community efforts aimed at cardiovascular risk factor prevention.

Our study has several strengths and limitations that should be considered when interpreting our findings. This is the first large study investigating the effect of AF on strokes in the American Indian race in a longitudinal analysis. Our broad inclusion criteria, using a common study cohort and large sample size, support the validity of our results. However, we acknowledge that HCUP relies on physician coding practices. Despite this, it is likely that such coding leads to lower sensitivity without sacrificing specificity, generally resulting in a reduced power to detect positive associations and minimizing the likelihood of false positive results. In addition, the assessment of stroke using *ICD-9* codes has been shown to have a high positive predictive value in administrative data.[45] Research using these methods, in particular the HCUP database, has proven to be a powerful tool and an accepted approach for large population studies.[7,10,20,46,47] Another limitation of this study is the reliance on self-report for race and ethnicity. Even though self-report has been shown to correlate well with genotype-confirmed continental ancestry,[48] previous work has shown that American Indian individuals may be misclassified in administrative patient discharge data.[49,50] Our analyses may also be prone to selection bias. By lacking outpatient clinic encounters, it is possible that a higher number of non-American Indian patients were diagnosed with nonacute strokes in the outpatient setting when compared with American Indian patients, or in the opposite case where we may have underestimated the relative stroke burden among American Indian individuals. In addition, our analyses did not include adjustment for anticoagulation status or data on anticoagulation prescribing patterns across racial and ethnic groups. Although this would offer insight into the mechanism of the observations, it would not necessarily negate the conclusions. Finally, as this was an observational study, we cannot exclude residual or unmeasured confounding and therefore these results should not be interpreted as evidence of causal effects.

In conclusion, we observed that American Indian individuals with AF are at highest risk of nonhemorrhagic stroke. This persisted after multivariable adjustment for known conventional confounders. Furthermore, as AF did not accentuate the increased risk for stroke, these findings are suggestive of an unidentified characteristic, including those possibly related to genetic differences or environmental exposures that increase the risk of stroke of American Indian individuals in general, whether or not AF is present.

ARTICLE INFORMATION

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Affiliations

From the Section of Cardiac Electrophysiology, Division of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, CO (J.M.S.); The Department of General Internal Medicine, Cleveland Clinic, OH (S.E.J.); The Section of Cardiac Electrophysiology, Division of Cardiology (T.A.D., Z.H.T., G.N., G.M.M.) and The Department of Epidemiology and Biostatistics, University of California, San Francisco, CA (E.V.).

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Supplementary Material

Table S1
Figures S1–S2

REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation*. 2020;141:e139–e596.
2. Centers for Disease Control and Prevention. Prevalence and most common causes of disability among adults - United States, 2005. *Morb Mortal Wkly Rep*. 2009;58:421–426.
3. Howard VJ, Kleindorfer DO, Judd SE, McClure LA, Safford MM, Rhodes JD, Cushman M, Moy CS, Soliman EZ, Kissela BM, et al. Disparities in stroke incidence contributing to disparities in stroke mortality. *Ann Neurol*. 2011;69:619–627. DOI: 10.1002/ana.22385.
4. Morgenstern LB, Smith MA, Lisabeth LD, Risser JMH, Uchino K, Garcia N, Longwells PJ, McFarling DA, Akuwumi O, Al-Wabil A, et al. Excess stroke in Mexican Americans compared with non-Hispanic Whites: the Brain Attack Surveillance in Corpus Christi Project. *Am J Epidemiol*. 2004;160:376–383. DOI: 10.1093/aje/kwh225.
5. White H, Boden-Albala B, Wang C, Elkind MSV, Rundek T, Wright CB, Sacco RL. Ischemic stroke subtype incidence among whites, blacks, and Hispanics. *Circulation*. 2005;111:1327–1331. DOI: 10.1161/01.CIR.0000157736.19739.D0.
6. Zhang Y, Galloway JM, Welty TK, Wiebers DO, Whisnant JP, Devereux RB, Kizer JR, Howard BV, Cowan LD, Yeh J, et al. Incidence and risk factors for stroke in american indians the strong heart study. *Circulation*. 2008;118:1577–1584. DOI: 10.1161/CIRCULATIONAHA.108.772285.
7. Dewland TA, Olgin JE, Vittinghoff E, Marcus GM. Incident atrial fibrillation among Asians, Hispanics, blacks, and whites. *Circulation*. 2013;128:2470–2477. DOI: 10.1161/CIRCULATIONAHA.113.002449.
8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983–988. DOI: 10.1161/01.STR.22.8.983.
9. Wang TJ, Massaro JM, Levy D, Vasan RS, Wolf PA, D'Agostino RB, Larson MG, Kannel WB, Benjamin EJ. A risk score for predicting stroke or death in individuals with new-onset atrial fibrillation in the community: the Framingham heart study. *J Am Med Assoc*. 2003;290:1049–1056. DOI: 10.1001/jama.290.8.1049.
10. Sanchez JM, Jolly SE, Dewland TA, Tseng ZH, Nah G, Vittinghoff E, Marcus GM. Incident atrial fibrillation among American Indians in California. *Circulation*. 2019;140:1605–1606. DOI: 10.1161/CIRCULATIONAHA.119.042882.
11. Kabra R, Cram P, Girotra S, Vaughan SM. Effect of race on outcomes (Stroke and Death) in patients >65 years with atrial fibrillation. *Am J Cardiol*. 2015;116:230–235.
12. Simpson JR, Zahuranec DB, Lisabeth LD, Sánchez BN, Skolarus LE, Mendizabal JE, Smith MA, Garcia NM, Morgenstern LB. Mexican Americans with atrial fibrillation have more recurrent strokes than do non-hispanic whites. *Stroke*. 2010;41:2132–2136. DOI: 10.1161/STROKEAHA.110.589127.
13. Kabra R, Girotra S, Vaughan SM. Refining stroke prediction in atrial fibrillation patients by addition of African-American ethnicity to CHA2DS2-VASc score. *J Am Coll Cardiol*. 2016;68:461–470.
14. Van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *J Am Med Assoc*. 2002;288:2441–2448. DOI: 10.1001/jama.288.19.2441.
15. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146:857–867.
16. Soliman EZ, Safford MM, Muntner P, Khodneva Y, Dawood FZ, Zakai NA, Thacker EL, Judd S, Howard VJ, Howard G, et al. Atrial fibrillation and the risk of myocardial infarction. *JAMA Intern Med*. 2014;174:107–114. DOI: 10.1001/jamainternmed.2013.11912.
17. Bansal N, Fan D, Hsu CY, Ordonez JD, Marcus GM, Go AS. Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. *Circulation*. 2013;127:569–574. DOI: 10.1161/CIRCULATIONAHA.112.123992.
18. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, Anderson JL, Muhlestein JB, Horne BD, Lappe DL, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm*. 2010;7:433–437. DOI: 10.1016/j.hrthm.2009.12.004.
19. Breathett K, Sims M, Gross M, Jackson EA, Jones EJ, Navas-Acien A, Taylor H, Thomas KL, Howard BV. Cardiovascular health in American Indians and Alaska Natives: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e948–e959. DOI: 10.1161/CIR.0000000000000773.
20. Whitman IR, Agarwal V, Nah G, Dukes JW, Vittinghoff E, Dewland TA, Marcus GM. Alcohol abuse and cardiac disease. *J Am Coll Cardiol*. 2017;69:13–24. DOI: 10.1016/j.jacc.2016.10.048.

21. Kleindorfer D, Broderick J, Khoury J, Flaherty M, Woo D, Alwell K, Moomaw CJ, Schneider A, Miller R, Shukla R, et al. The unchanging incidence and case-fatality of stroke in the 1990s: a population-based study. *Stroke*. 2006;37:2473–2478. DOI: 10.1161/01.STR.0000242766.65550.92.
22. Kissela B, Schneider A, Kleindorfer D, Khoury J, Miller R, Alwell K, Woo D, Szaflarski J, Gebel J, Moomaw C, et al. Stroke in a biracial population: the excess burden of stroke among blacks. *Stroke*. 2004;35:426–431. DOI: 10.1161/01.STR.0000110982.74967.39.
23. Jones MR, Horner RD, Edwards LJ, Hoff J, Armstrong SB, Smith-Hammond CA, Matchar DB, Oddone EZ. Racial variation in initial stroke severity. *Stroke*. 2000;31:563–567. DOI: 10.1161/01.STR.31.3.563.
24. Dukes JW, Marcus GM. Atrial fibrillation begets myocardial infarction. *JAMA Intern Med*. 2014;174:5–7.
25. Mongkhon P, Fanning L, Lau WCY, Tse G, Lau KK, Wei L, Kongkaew C, Wong ICK. Oral anticoagulant and reduced risk of dementia in patients with atrial fibrillation: a population-based cohort study. *Heart Rhythm*. 2020;17:706–713. DOI: 10.1016/j.hrthm.2020.01.007.
26. Welty TK, Lee ET, Yeh J, Cowan LD, Go O, Fabsitz RR, Le NA, Oopik AJ, Robbins DC, Howard BV. Cardiovascular disease risk factors among American Indians: the strong heart study. *Am J Epidemiol*. 1995;142:269–287. DOI: 10.1093/oxfordjournals.aje.a117633.
27. Howard BV, Lee ET, Yeh JL, Go O, Fabsitz RR, Devereux RB, Welty TK. Hypertension in adult American Indians: the strong heart study. *Hypertension*. 1996;28:256–264. DOI: 10.1161/01.HYP.28.2.256.
28. Howard BV, Lee ET, Cowan LD, Devereux RB, Galloway JM, Go OT, Howard WJ, Rhoades ER, Robbins DC, Sievers ML, et al. Rising tide of cardiovascular disease in American Indians: the strong heart study. *Circulation*. 1999;99:2389–2395. DOI: 10.1161/01.CIR.99.18.2389.
29. Lee ET, Cowan LD, Welty TK, Sievers M, Howard WJ, Oopik A, Wang W, Yeh J, Devereux RB, Rhoades ER, et al. All-cause mortality and cardiovascular disease mortality in three American Indian Populations, aged 45–74 Years, 1984–1988: the strong heart study. *Am J Epidemiol*. 1998;147:995–1008.
30. Brown RD, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Stroke incidence, prevalence, and survival: secular trends in Rochester, Minnesota, through 1989. *Stroke*. 1996;27:373–380.
31. Broderick J, Brott T, Kothari R, Miller R, Khoury J, Pancioli A, Gebel J, Mills D, Minneci L, Shukla R. The greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. *Stroke*. 1998;29:415–421. DOI: 10.1161/01.STR.29.2.415.
32. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. *Circulation*. 2014;130:e199–e267.
33. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154:1121–1201. DOI: 10.1016/j.chest.2018.07.040.
34. Howard VJ. Reasons underlying racial differences in stroke incidence and mortality. *Stroke*. 2013;44:S126–S128. DOI: 10.1161/STROKEAHA.111.000691.
35. Ong KL, Cheung BMY, Man YB, Lau CP, Lam KSL. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension*. 2007;49:69–75. DOI: 10.1161/01.HYP.0000252676.46043.18.
36. Parrinello CM, Rastegar I, Godino JG, Miedema MD, Matsushita K, Selvin E. Prevalence of and racial disparities in risk factor control in older adults with diabetes: the atherosclerosis risk in communities study. *Diabetes Care*. 2015;38:1290–1298. DOI: 10.2337/dc15-0016.
37. Dickson VV, Knafl GJ, Wald J, Riegel B. Racial differences in clinical treatment and self-care behaviors of adults with chronic heart failure. *J Am Heart Assoc*. 2015;4:e001561. DOI: 10.1161/JAHA.114.001561.
38. Georgakis MK, Gill D, Rannikmäe K, Traylor M, Anderson CD, Lee J-M, Kamatani Y, Hopewell JC, Worrall BB, Bernhagen J, et al. Genetically determined levels of circulating cytokines and risk of stroke: role of monocyte chemoattractant protein-1. *Circulation*. 2019;139:256–268. DOI: 10.1161/CIRCULATIONAHA.118.035905.
39. Rouhl RPW, Damoiseaux JGMC, Lodder J, Theunissen ROMFIH, Knottnerus ILH, Staals J, Henskens LHG, Kroon AA, de Leeuw PW, Tervaert JWC, et al. Vascular inflammation in cerebral small vessel disease. *Neurobiol Aging*. 2012;33:1800–1806. DOI: 10.1016/j.neurobiolaging.2011.04.008.
40. Esenwa CC, Elkind MS. Inflammatory risk factors, biomarkers and associated therapy in ischaemic stroke. *Nat Rev Neurol*. 2016;12:594–604.
41. Karas MG, Devereux RB, Wiebers DO, Whisnant JP, Best LG, Lee ET, Howard BV, Roman MJ, Umans JG, Kizer JR. Incremental value of biochemical and echocardiographic measures in prediction of ischemic stroke: the strong heart study. *Stroke*. 2012;43:720–726. DOI: 10.1161/STROKEAHA.111.631168.
42. Warne D, Frizzell LB. American Indian Health Policy: historical trends and contemporary issues. *Am J Public Health*. 2014;104:S263–S267. DOI: 10.2105/AJPH.2013.301682.
43. Arias E, Xu J, Jim MA. Period life tables for the non-Hispanic American Indian and Alaska Native population, 2007–2009. *Am J Public Health*. 2014;104:S312–S319. DOI: 10.2105/AJPH.2013.301635.
44. Indian Health Services. Disparities | Fact Sheets. Available at https://www.ihs.gov/newsroom/factsheets/disparities/. Accessed May 21, 2019.
45. Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. *Pharmacoepidemiol Drug Saf*. 2008;17:20–26. DOI: 10.1002/pds.1518.
46. Birkmeyer JD, Siewers AE, Finlayson EVA, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. *N Engl J Med*. 2002;346:1128–1137. DOI: 10.1056/NEJMsa012337.
47. Gialdini G, Nearing K, Bhave PD, Bonuccelli U, Iadecola C, Healey JS, Kamel H. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *JAMA*. 2014;312:616. DOI: 10.1001/jama.2014.9143.
48. Wang H, Haiman CA, Kolonel LN, Henderson BE, Wilkens LR, Le Marchand L, Stram DO. Self-reported ethnicity, genetic structure and the impact of population stratification in a multiethnic study. *Hum Genet*. 2010;128:165–177. DOI: 10.1007/s00439-010-0841-4.
49. Rhoades DA. Racial misclassification and disparities in cardiovascular disease among American Indians and Alaska Natives. *Circulation*. 2005;111:1250–1256. DOI: 10.1161/01.CIR.0000157735.25005.3F.
50. Kressin NR, Chang B-H, Hendricks A, Kazis LE. Agreement between administrative data and patients' self-reports of race/ethnicity. *Am J Public Health*. 2003;93:1734–1739. DOI: 10.2105/AJPH.93.10.1734.

SUPPLEMENTAL MATERIAL

Table S1. International Classification of Diseases-9th Edition (ICD-9) and Current Procedural Terminology (CPT) Codes Used for Disease Identification.

Diagnosis	ICD-9 / CPT Codes	
Atrial fibrillation	ICD-9	427.31
Hypertension	ICD-9	401.X, 402.X, 403.X, 404.X, 405.X, 437.2
Diabetes mellitus	ICD-9	249.X, 250.X, 790.X, 791.5, 791.6, V458.5, V539.1, V654.6
Coronary artery disease	ICD-9	36.01, 36.02, 36.03, 36.05, 36.09, 36.1X, 411.0, 411.1, 411.8, 411.89, 412, 413.X, 414.X, 429.7, V458.2
Heart failure	ICD-9	402.01, 402.11, 402.91, 404.91, 404.93, 425.X, 428.X
Cardiothoracic surgery	ICD-9	35.3X, 35.41, 35.42, 35.50, 35.51, 35.52, 35.53, 35.54, 35.60, 35.61, 35.62, 35.63, 35.70, 35.71, 35.72, 35.73, 36.1X, 37.10, 37.11, 37.12, 37.24, 37.25, 37.31, 37.32, 37.33, 37.35, 37.40
Valvular disease	ICD-9	394.X, 395.X, 396.X, 397.0, 397.1, 424.0, 424.1, 424.2, 424.3, V422, V433
Pulmonary disease	ICD-9	494.2X, 491.8, 491.9, 492.0, 492.8, 494, 494.0, 494.1, 496
Chronic kidney disease	ICD-9	39.93, 54.98, 585.X, V420, V451, V451.1, V451.2, V560, V561, V562, V563.1, V563.2, V568, V56
	CPT	90921, 90925, 90935, 90937, 90945, 90947, 90989, 90993
Obesity	ICD-9	278.X
Alcohol use	ICD-9	291.0, 291.1, 291.3, 291.4, 291.81, 303, 303.0, 303.00, 303.01, 303.02, 303.03, 303.9, 303.90, 303.91, 303.92, 303.93, 305.0
Active smoking	ICD-9	305.1
Obstructive sleep apnea	ICD-9	327.20, 327.21, 327.22, 327.23, 327.24, 327.25, 327.26, 327.27, 327.29, 780.51, 780.53, 780.57
Non-hemorrhagic stroke	ICD-9	434.91, 434.11, 434.01

Figure S1. Study Sample Selection.

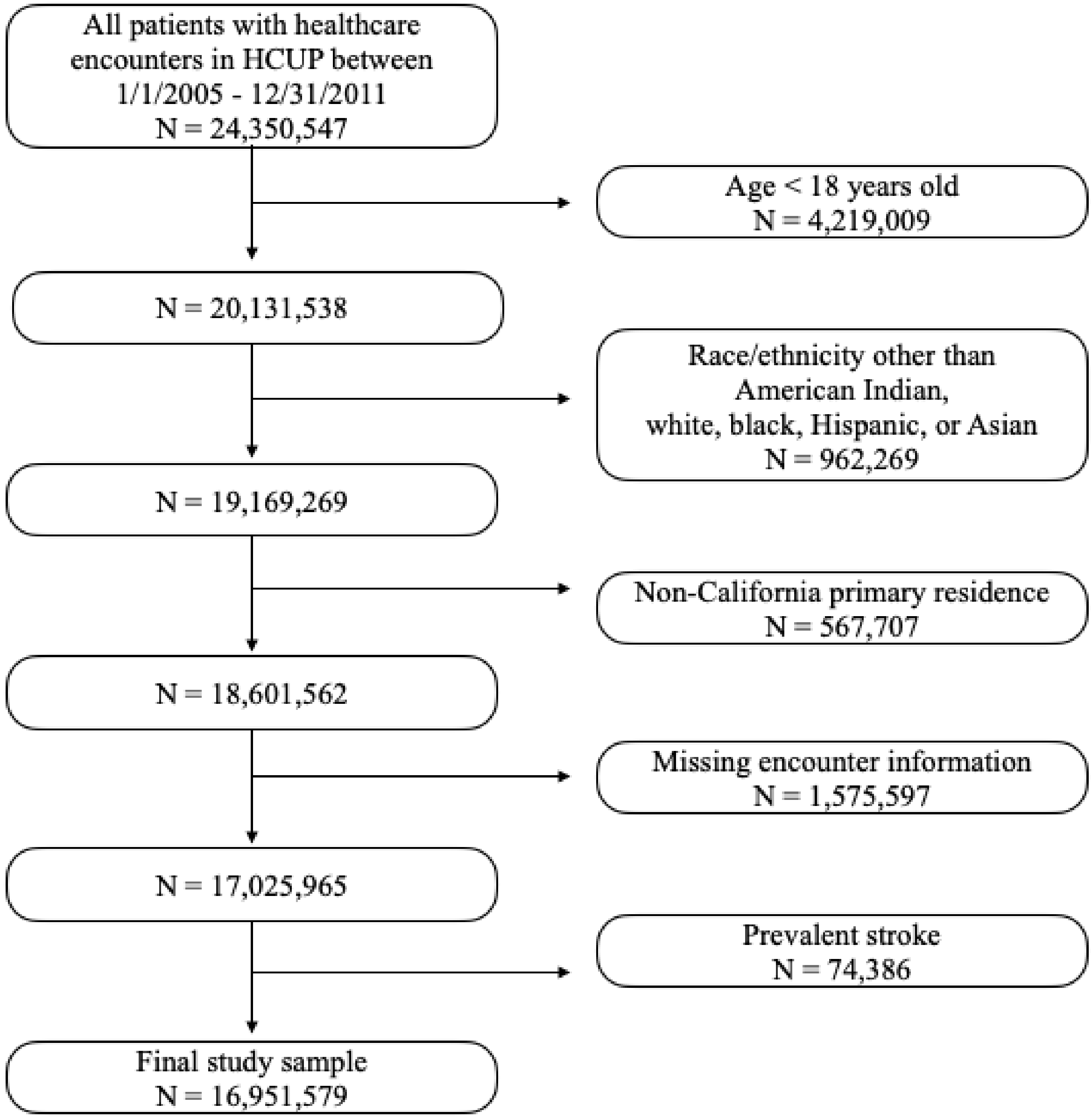
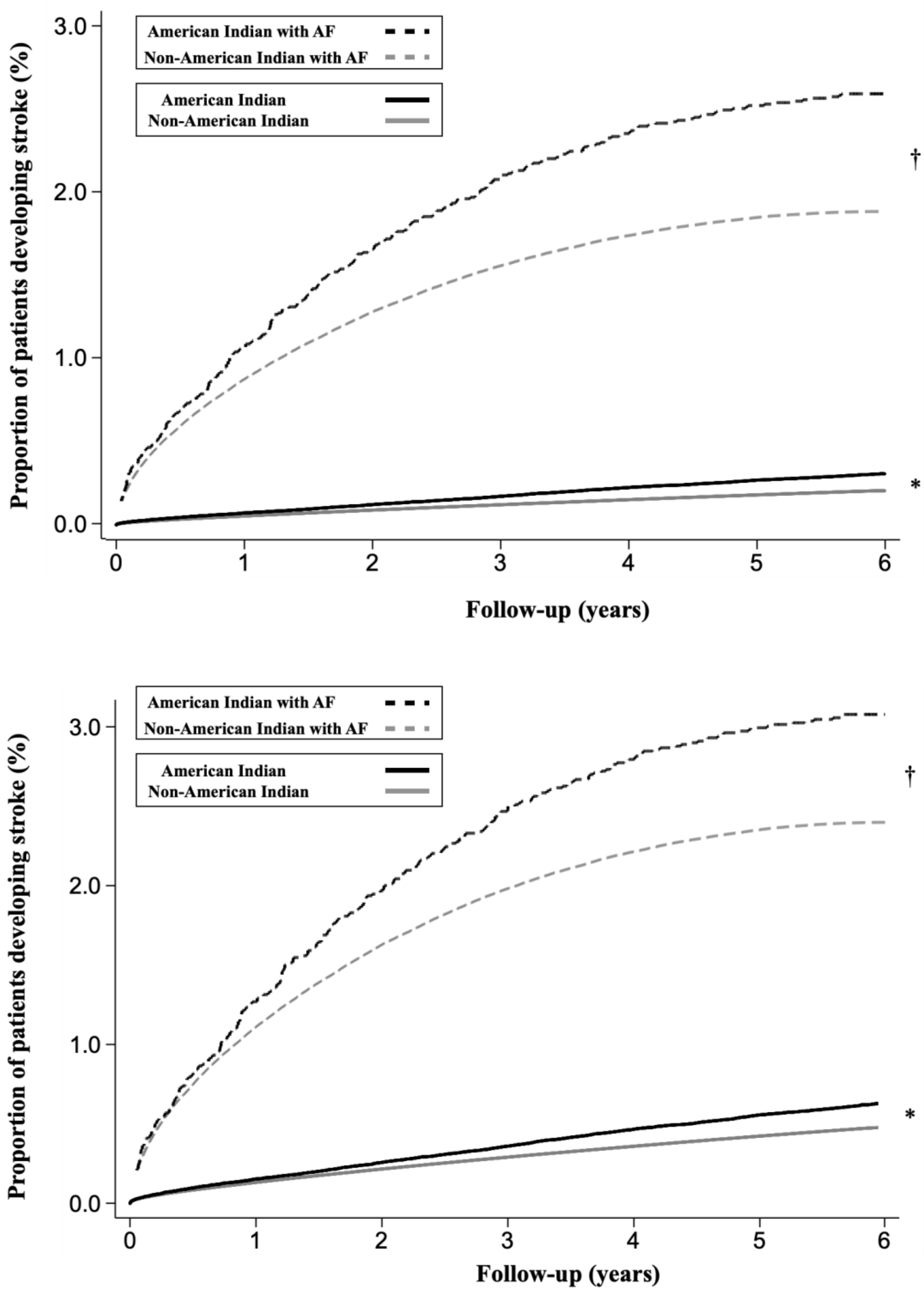


Figure S2. Adjusted Kaplan Meier Curves for Incident Non-Hemorrhagic Stroke in American Indian and Non-American Indian Patients with and without AF.



Top: Analysis includes only the Emergency Department and State Inpatient Databases – the Ambulatory Surgery Database was excluded. Bottom: Analysis includes only those over the age of 35 with at least two encounters. The curves are adjusted for age, sex, income level, insurance payer, hypertension, diabetes, coronary artery disease, congestive heart failure, cardiac surgery, valvular heart disease, chronic kidney disease, smoking, obstructive sleep apnea, pulmonary disease, and alcohol use. AF indicates atrial fibrillation. * Comparison between American Indians to non-American Indians, P value < 0.0001. † Comparison between American Indians with AF to non-American Indians with AF, P value < 0.0001.