Increasing atrial fibrillation prevalence in acute ischemic stroke and TIA

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ABSTRACT

Objective: To evaluate trends in atrial fibrillation (AF) prevalence in acute ischemic stroke (AIS) and TIA in the United States.

Methods: We used the Nationwide Inpatient Sample to retrospectively compute weighted prevalence of AF in AIS (n = 4,355,140) and TIA (n = 1,816,459) patients admitted to US hospitals from 2004 to 2013. Multivariate-adjusted models were used to evaluate the association of AF with clinical factors, mortality, length of stay, and cost.

Results: From 2004 to 2013, AF prevalence increased by 22% in AIS (20%–24%) and by 38% in TIA (12%–17%). AF prevalence varied by age (AIS: 6% in 50–59 vs 37% in ≥80 years; TIA: 4% in 50–59 vs 24% in ≥80 years), sex (AIS: male 19% vs female 25%; TIA: male 15% vs female 14%), race (AIS: white 26% vs black 12%), and region (AIS: Northeast 25% vs South 20%). Advancing age, female sex, white race, high income, and large hospital size were associated with increased odds of AF in AIS. AF in AIS was a risk factor for in-hospital death (odds ratio 1.93, 95% confidence interval 1.89–1.98) but mortality in AIS with AF decreased from 11.6% to 8.3% ($p < 0.001$). Compared to no AF, AF was associated with increased cost of \$2,310 and length of stay 1.1 days in AIS.

Conclusions: AF prevalence in AIS and TIA has continued to increase. Disparity in AF prevalence in AIS and TIA exists by patient and hospital factors. AF is associated with increased mortality in AIS. Innovative AIS preventive strategies are needed in patients with AF, especially in the elderly.

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GLOSSARY

AF = atrial fibrillation; **AHRQ** = Agency for Healthcare Research and Quality; **AIS** = acute ischemic stroke; **CCI** = Charlson Comorbidity Index; **CI** = confidence interval; **HCUP** = Health Care Utilization Project; **ICD-9** = *International Classification of Diseases-9*; **LOS** = length of stay; **NIS** = Nationwide Inpatient Sample; **OR** = odds ratio; **PPV** = positive predictive value.

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia¹ and is associated with a 5-fold increased risk of acute ischemic stroke (AIS).² Between 2.7 and 6.1 million people in the United States have AF and as the US population ages, this number is projected to more than double by 2050.³ Accurate understanding of variations in AF prevalence in AIS is important for discerning changes in the epidemiologic, clinical, and social characteristics of AIS over time, but contemporary large-scale data on the burden of AF-associated AIS in the United States are lacking. While AF-related hospitalizations in the United States increased over the last decade,⁴ it remains unclear what direction and by how much AF-associated AIS changed over this period.

The primary aim of our study is to quantify and describe trends in the prevalence of AF in hospitalized AIS and TIA patients in the United States from 2004 to 2013. We secondarily evaluated the association of AF with other socioeconomic and hospital-level factors in AIS and evaluated the current association of comorbid AF with in-hospital mortality, length of stay (LOS), and hospitalization cost in AIS.

METHODS Data for this study were obtained from the 2004–2013 Nationwide Inpatient Sample (NIS). The NIS is maintained as part of the Health Care Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ). It is the largest

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Supplemental data
at Neurology.org

all-payer inpatient care database in the United States and comprises a 20% stratified random sample of all US hospital discharges. Each discharge in the NIS is de-identified so all discharges were considered to be independent. The unit for this analysis was each discharge rather than each individual. Further details on the NIS design are available at hcup-us.ahrq.gov.

Standard protocol approvals, registrations, and patient consents. We received the exemption status to conduct this study from the University of Miami institutional review board.

Study population. From 78,327,564 hospitalizations contained in the NIS from 2004 to 2013, we identified all adult primary AIS (n = 883,122) and TIA (n = 368,577) admissions by querying the NIS database using ICD-9 codes. In accordance with American Heart Association current definitions,⁵ AIS patients were identified using codes in the range 433.x1, 434.x1, and 436, and TIA patients were identified using codes 435.x. These codes have a combined positive predictive value (PPV) of >85% for AIS and up to 89% for TIA in several studies.⁶ Patients with codes 433.x0 and 434.x0 were excluded (n = 264,787), as these make no mention of cerebral infarction or ischemia. Additional patients <18 years of age (n = 1,791) were excluded.

Definition of outcomes. Primary outcome in this study was AF and this was defined as present if participants had ICD-9 code (427.31) for AF in any of their secondary discharge diagnoses fields. This code has a specificity of 98% and PPV of 89% for AF.⁷ Secondary outcomes include in-hospital mortality and this was studied using the NIS variable “died” and LOS defined using variable “LOS.” Hospitalization cost was calculated by multiplying total hospital charge in the NIS by cost-to-charge ratios provided as an additional file in the NIS. Calculated cost of each hospitalization was adjusted for inflation and expressed in terms of 2015 US dollars using coefficients obtained from the Bureau of Labor and Statistics website: bls.gov/data/inflation_calculator.htm.

Covariate assessment. Age was categorized into 18–39 years, and according to 10-year increments from 40 to 49 up to ≥80 years. Comorbidities associated with AIS hospitalization were identified by AHRQ comorbidity measures available in the NIS. AHRQ comorbidity measures identify different comorbidities using ICD-9-CM diagnoses and the diagnosis-related group that are not directly related to the principal diagnosis and are likely to have been present prior to hospitalization.⁴ CHA₂DS₂-VASc score, a validated point-based scoring system for estimating AIS risk in patients with AF using age, sex, and clinical factors including previous stroke, congestive heart failure, hypertension, diabetes mellitus, and vascular disease, was calculated for all patients using AHRQ comorbidity measures.⁸ The minimum possible CHA₂DS₂-VASc score in our cohort was 2 as all patients had either a stroke or TIA. The modified Charlson Comorbidity Index (CCI),⁹ a validated weighted comorbid disease severity score composed of 17 comorbid conditions including congestive heart failure, myocardial infarction, chronic pulmonary disease, cerebrovascular disease, dementia, diabetes with and without complications, liver disease, peptic ulcer disease, peripheral vascular disease, rheumatologic disease, renal disease, hemiplegia or paraplegia, malignancy, metastatic solid tumor, and AIDS, was calculated for all participants. Patients were subsequently categorized into 4 categories, including a CCI of 1, 2, 3, or ≥4, according to quartile of CCI scores.

Information on hospital characteristics including location, region, teaching status, and bed size were extracted. Total annual AIS admissions of hospitals were counted and hospitals were

grouped annually into tertiles based on their yearly stroke volumes.

Statistical analysis. Baseline characteristics of participants were summarized using descriptive statistics. Sampling weights provided in the NIS allow for calculation of total national estimates from the 20% of all admissions in the NIS.¹⁰ We used these weights to compute the overall unadjusted weighted national prevalence of AF in AIS and TIA patients. We calculated weighted prevalence in subgroups categorized by age, sex, race, household income, and hospital region. We evaluated trends in AF prevalence over time by constructing a logistic regression model with AF as the dependent variable and year of discharge as the independent variable, evaluated continuously, with significance of differences in trend over time assessed by using the Wald test.

We constructed univariate (model 1) and multivariate-adjusted logistic models (models 2 and 3) to evaluate the association of AF with other clinical plus hospital factors and to control for potential confounding. Model 2 was adjusted for demographic factors in addition to income, insurance status, year of discharge, and hospital characteristics: region (Northeast, Midwest, South, West), bed size (small, medium, large), stroke volume by tertile, and location/teaching status (rural, urban nonteaching, urban teaching). Model 3 was additionally adjusted for clinical factors with known association with AF. CHA₂DS₂-VASc scores and CCI were excluded from model 3 due to concern for collinearity.

We used logistic regression models adjusted for demographic, hospital, and comorbid factors to evaluate the relationship between AF and in-hospital death. To evaluate trends in mortality in AIS patients with comorbid AF, we restricted analysis to patients with AF and constructed multivariate models with death as outcome and year modeled as a continuous variable. Trends in AF mortality in AIS patients were again assessed using the Wald test.

We evaluated the relationship between AF and hospitalization cost and LOS in AIS by fitting generalized linear models with a gamma variance distribution and adjusted for patient and hospital factors.

A 2-tailed *p* value of <0.05 was required for statistical significance. All analyses were performed using Stata 13 (StataCorp, College Station, TX). We took into account the stratified cluster sampling of the NIS in all our models by use of Stata's SVY suite of commands, with use of the hospital as the primary sampling unit and use of applicable probability sampling weights for robust variance estimation in all multivariate models.

Missing variables. Most variables had missing values in <2.5% of participants, except for race and cost-to-charge ratio, which were missing in 16.6% and 3.8% of participants, respectively. Missing data were imputed to the dominant category for categorical variables and to the median for continuous variables.¹¹ Missing insurance status for those aged ≥65 years was imputed to Medicare. Missing cost data were handled using reweighting technique recommended by HCUP¹² and missing hospital variables such as teaching status (0.46%) and number of beds (0.46%) were excluded. Participants with missing race data were excluded in subgroup analysis stratified by race, but all multivariate models contained imputed race data. Main effect estimates were similar when missing variables were accounted for using Stata's MI suite of multiple imputation commands.

RESULTS The 883,122 AIS and 368,577 TIA patients identified in the NIS represent 4,355,140 weighted AIS and 1,816,459 weighted TIA

admissions from 2004 to 2013. A total of 22.1% (n = 962,230) of all weighted AIS and 14.2% (n = 258,429) of all weighted TIA cases over this period had AF. Baseline characteristics of patients with and without AF are summarized in table e-1 at Neurology.org. AIS patients with AF were relatively older, were more likely to be white, and had higher CCI and CHA₂DS₂-VASc scores compared to patients without AF (table e-1). A total of 57.9% of

all AIS patients with comorbid AF and 56.3% of all TIA patients with comorbid AF were ≥80 years of age (table e-1).

The proportion of AIS patients with comorbid AF increased from 19.7% in 2004 to 24.0% in 2013 (relative increase 21.7%, *p* value for trend <0.001) (table 1), while proportion of TIA with AF also increased from 12.3% to 17.0% over the same period (relative increase 38%, *p* value for trend <0.001) (table e-2).

Table 1 Weighted prevalence of atrial fibrillation (AF) in adult acute ischemic stroke patients hospitalized in the United States from 2004 to 2013 according to demographic and hospital characteristics

Variables	Total	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	<i>p</i> Trend
Total number ^a	883,122	87,662	84,006	84,300	82,710	89,326	84,166	90,226	97,506	90,824	92,396	NA
Weighted total number ^b	4,355,140	424,398	410,789	412,611	407,027	438,217	426,039	450,778	469,182	454,120	461,980	NA
Total % with AF	22.1	19.7	20.8	21.2	21.2	21.1	22.3	22.3	23.8	23.9	24.0	<0.001
Age, y, %												
<40	2.3	1.5	1.6	3.0	2.1	2.3	2.2	2.5	2.1	2.7	2.8	0.0196
40-49	3.6	3.1	2.9	3.5	3.2	3.1	3.6	3.8	4.0	4.2	4.5	<0.0001
50-59	6.4	5.5	5.3	5.9	6.1	5.8	6.2	6.5	7.4	7.4	7.1	<0.0001
60-69	12.6	10.7	11.7	11.9	11.8	11.8	12.5	12.9	13.3	14.2	14.1	<0.0001
70-79	23.5	21.0	21.7	22.7	22.6	22.4	23.6	24.2	25.2	25.4	25.8	<0.0001
≥80	37.3	32.2	33.8	34.8	35.3	35.8	37.9	38.5	40.6	41.3	41.9	<0.0001
Sex, %												
Male	19.2	17.3	17.9	18.3	18.2	18.0	18.9	19.2	20.8	21.1	21.1	<0.0001
Female	24.7	21.7	23.1	23.6	23.8	23.8	25.3	25.2	26.4	26.5	26.8	<0.0001
Race, %												
White	25.7	23.1	24.0	24.7	25.3	24.4	25.8	26.0	27.3	27.2	27.3	<0.0001
Black	11.7	10.9	10.2	11.2	10.9	10.9	11.5	11.4	12.3	13.2	12.8	<0.0001
Hispanic	16.2	14.3	14.7	15.6	13.0	15.1	16.4	15.5	18.0	17.9	19.2	<0.0001
Other	19.8	16.0	16.9	19.5	18.0	19.6	20.3	20.2	20.5	22.1	21.4	<0.0001
Income category												
\$1-\$38,999	18.4	17.0	17.3	17.5	17.7	17.9	18.1	18.1	19.0	20.4	20.7	<0.0001
\$39,000-\$47,999	21.6	19.3	20.3	20.8	20.8	20.6	21.4	22.4	23.4	23.3	23.5	<0.0001
\$48,000-\$62,999	23.6	21.1	22.3	22.5	22.8	22.1	24.2	23.6	25.5	25.1	25.6	<0.0001
≥\$63,000	26.5	23.2	24.6	25.6	25.3	25.7	27.2	27.2	28.9	29.0	28.2	<0.0001
Insurance												
Medicare	27.8	24.4	25.7	26.5	26.7	26.7	28.3	28.6	30.2	30.2	30.5	<0.0001
Medicaid	8.7	7.3	8.0	9.1	7.6	8.0	8.8	9.3	9.2	9.3	9.6	<0.0001
Private	12.0	10.3	10.2	10.5	11.7	12.0	12.7	12.5	13.0	13.3	12.9	<0.0001
Self-pay	6.8	6.7	5.8	6.4	6.5	7.2	6.7	6.4	7.0	7.4	7.3	0.0451
Other	12.1	11.5	10.8	9.6	10.5	12.7	11.4	12.9	12.6	13.8	13.5	0.0005
Hospital region, %												
Northeast	24.8	22.7	24.3	24.4	24.3	24.3	24.9	23.5	25.6	27.0	26.4	<0.0001
Midwest	22.0	18.6	20.5	21.1	21.1	21.1	22.5	22.7	23.9	24.1	24.3	<0.0001
South	20.0	18.3	18.5	19.1	19.0	18.9	19.9	20.5	21.8	22.0	21.7	<0.0001
West	24.2	22.1	22.6	22.7	23.3	23.4	24.9	24.7	25.8	25.1	26.7	<0.0001

^aRepresents actual number of patients contained in the Nationwide Inpatient Sample.

^bRepresents projected total national estimates obtained by applying sampling weights to the Nationwide Inpatient Sample dataset.

Age, sex, and regional differences in AF prevalence in AIS and TIA patients. AF prevalence in AIS and TIA increased with age. With each 10-year increase in age, AF prevalence increased by a factor >1.5 -fold in both AIS and TIA patients up to age ≥ 80 years (table 1 and table e-2). AF was more prevalent in women with AIS compared to men (24.7% vs 19.2%) (table 1) but slightly more prevalent in men with TIA compared to women (15.0% in men vs 13.7% in women) (table e-2). AF was more prevalent in whites compared to blacks and Hispanics in both AIS and TIA patients (table 1 and table e-2).

Figure 1 shows the temporal prevalence of AF in AIS and figure 2 shows the prevalence of AF in TIA in subgroups categorized by age, sex, race, and income,

respectively. AF prevalence consistently increased across all subgroups with increasing year from 2004 to 2013 (p value for trend <0.05) in both AIS and TIA (figures 1 and 2, tables 1 and e-2) except in self-paying TIA patients (p value for trend = 0.7527) (table e-2). Interestingly, AF was more prevalent in AIS and TIA patients with household income $\geq \$63,000$ compared to those who earned less (all p values for comparison <0.001) (figures 1 and 2). AF was also more prevalent in the Northeast and West in all years compared to the Midwest and South in both AIS and TIA (p value for comparison <0.001) (table 1 and table e-2), but because more AIS admissions occurred in the South (table e-1) and the South accounted for 37.2% of all AF-associated strokes (compared to 20.1%, 22.9%, and 19.7% in

Figure 1 Weighted prevalence of atrial fibrillation in adult acute ischemic stroke patients hospitalized in the United States from 2004 to 2013

Prevalence according to (A) age, (B) sex, (C) race, and (D) income.

Figure 2 Weighted prevalence of atrial fibrillation in adult TIA patients hospitalized in the United States from 2004 to 2013

Prevalence according to (A) age, (B) sex, (C) race, and (D) income.

the Northeast, Midwest, and West, respectively), significantly more AF-associated stroke admissions occurred in the South compared to other regions.

Association of AF in AIS with demographic, socioeconomic, and hospital variables. The temporally increasing trend in AF prevalence with year persisted even after multivariate adjustment. With each increase in year over the study period, odds of prevalent AF increased 5% (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.04–1.06) (table 2).

Sociodemographic factors associated with increased AF prevalence after adjustment included increasing age, white race, female sex, high income, and Medicare insurance (table 2). Odds of comorbid AF in AIS were lower in hospitals in the lowest tertile for yearly stroke volume, hospitals with small bed size

compared to larger hospitals, rural hospitals compared to urban hospitals, and hospitals located in the South and Midwest regions compared to those in the Northeast (table 2).

Association of AF with mortality, hospitalization cost, and LOS. In-hospital mortality rates were higher in AF patients compared to non-AF patients across the entire study period (figure e-1). From 2004 to 2013, overall in-hospital mortality in AIS patients with AF declined from 11.6% to 8.3% (p value for trend <0.001). After multivariate adjustment, AF was associated with 93% increased odds of death compared to no AF (OR 1.93, 95% CI 1.89–1.98) (table 3), but with each year, the odds of death in AIS patients with comorbid AF decreased by 5% (OR 0.95, 95% CI 0.94–0.95) (table 3).

Table 2 Association of comorbid atrial fibrillation (AF) with other clinical factors in hospitalized acute ischemic stroke patients in the United States between 2004 and 2013

Variable	Unadjusted model			Multivariate model 1 ^a			Multivariate model 2 ^b		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Year, per unit increase in year	1.03	1.02-1.03	<0.001	1.04	1.04-1.04	<0.001	1.05	1.05-1.05	<0.001
Age, y									
Per unit increase in age	1.07	1.07-1.07	<0.001	1.06	1.06-1.06	<0.001	1.05	1.05-1.05	<0.001
40-49 vs <40	1.60	1.43-1.78	<0.001	1.64	1.47-1.82	<0.001	1.72	1.54-1.92	<0.001
50-59 vs <40	2.90	2.62-3.20	<0.001	2.74	2.46-3.05	<0.001	3.09	2.80-3.41	<0.001
60-69 vs <40	6.12	5.56-6.76	<0.001	5.28	4.75-5.87	<0.001	5.82	5.27-6.43	<0.001
70-79 vs <40	13.04	11.84-14.37	<0.001	10.3	9.26-11.45	<0.001	11.0	9.97-12.15	<0.001
≥80 vs <40	25.26	22.93-27.84	<0.001	19.4	17.42-21.55	<0.001	18.20	16.48-20.10	<0.001
Sex, female vs male	1.38	1.36-1.40	<0.001	1.07	1.05-1.08	<0.001	1.05	1.04-1.06	<0.001
Race									
Black vs white	0.41	0.40-0.42	<0.001	0.59	0.57-0.60	<0.001	0.57	0.56-0.59	<0.001
Hispanic vs white	0.60	0.57-0.62	<0.001	0.75	0.72-0.77	<0.001	0.77	0.75-0.80	<0.001
Others vs white	0.76	0.73-0.79	<0.001	0.84	0.82-0.87	<0.001	0.88	0.85-0.91	<0.001
Income									
\$39,000-\$47,999 vs <\$39,000	1.22	1.20-1.25	<0.001	1.07	1.05-1.09	<0.001	1.08	1.06-1.10	<0.001
\$48,000-\$62,999 vs <\$39,000	1.37	1.34-1.40	<0.001	1.10	1.08-1.12	<0.001	1.12	1.10-1.14	<0.001
≥\$63,000 vs <\$39,000	1.60	1.56-1.64	<0.001	1.19	1.16-1.21	<0.001	1.21	1.18-1.23	<0.001
Insurance									
Medicaid vs Medicare	0.25	0.24-0.26	<0.001	0.85	0.82-0.88	<0.001	0.86	0.82-0.88	<0.001
Private vs Medicare	0.35	0.34-0.36	<0.001	0.86	0.85-0.88	<0.001	0.90	0.89-0.92	<0.001
Self-pay vs Medicare	0.19	0.18-0.20	<0.001	0.72	0.69-0.76	<0.001	0.76	0.72-0.79	<0.001
Other vs Medicare	0.36	0.34-0.38	<0.001	0.86	0.82-0.90	<0.001	0.89	0.85-0.94	<0.001
Hospital region									
Midwest vs northeast	0.86	0.83-0.89	<0.001	0.91	0.89-0.94	<0.001	0.86	0.84-0.89	<0.001
South vs northeast	0.76	0.73-0.79	<0.001	0.92	0.90-0.95	<0.001	0.90	0.88-0.92	<0.001
West vs northeast	0.97	0.94-1.01	0.114	1.04	1.01-1.07	0.008	1.06	1.03-1.09	<0.001
Hospital location/teaching status									
Urban nonteaching vs rural	1.09	1.06-1.12	<0.001	1.10	1.07-1.13	<0.001	1.09	1.06-1.12	<0.001
Urban teaching vs rural	1.06	1.03-1.10	<0.001	1.21	1.17-1.25	<0.001	1.20	1.16-1.24	<0.001
Stroke volume per year ^c									
Middle tertile vs lowest tertile	1.05	1.02-1.08	<0.001	1.06	1.04-1.09	<0.001	1.06	1.04-1.09	<0.001
Upper tertile vs lower tertile	1.06	1.03-1.09	<0.001	1.11	1.08-1.15	<0.001	1.11	1.08-1.15	<0.001
Hospital bed size ^d									
Medium vs small	1.00	0.97-1.04	0.881	1.09	1.06-1.12	<0.001	1.09	1.06-1.12	<0.001
Large vs small	1.00	0.97-1.04	0.813	1.13	1.10-1.17	<0.001	1.13	1.10-1.17	<0.001
CHA ₂ DS ₂ VASc	1.58	1.58-1.59	<0.001	1.22	1.21-1.23	<0.001			
Modified CCI									
CCI 2 vs CCI 1	1.17	1.15-1.16	<0.001	1.14	1.13-1.16	<0.001			

Continued

Table 2 Continued

Variable	Unadjusted model			Multivariate model 1 ^a			Multivariate model 2 ^b		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
CCI 3 vs CCI 1	1.49	1.46-1.52	<0.001	1.31	1.29-1.34	<0.001			
CCI ≥4 vs CCI 1	1.69	1.66-1.72	<0.001	1.45	1.43-1.48	<0.001			

Abbreviations: CCI = Charlson Comorbidity Index; CI = confidence interval; OR = odds ratio.

^aMultivariate model 1: obtained from logistic regression model accounting for survey design and adjusted for age, race, sex, income, insurance status, year, hospital region, hospital location/teaching status, hospital bed size, and hospital stroke volume.

^bMultivariate model 2: multivariate model 1 plus myocardial infarction, congestive heart failure, coronary heart disease, valvular heart disease, chronic lung disease, peripheral vascular disease, renal failure, pulmonary circulation disorders, uncomplicated diabetes, complicated diabetes, hypothyroidism, hyperthyroidism, hypertension, drug abuse, smoking, solid cancer, metastatic cancer, AIDS, coagulopathy, liver disease, dyslipidemia, and obesity.

^cHospitals categorized into tertiles based on their total number of stroke hospitalizations per year. Annual stroke admissions for each hospital varied from year to year so absolute numbers for each tertile range were not constant over time.

^dNumber of short-term acute beds in a hospital. See full bed categorization detailed at hcup-us.ahrq.gov/db/vars/hosp_bedsizes/nisnote.jsp.

AF was also associated with ≈\$2,300 increased hospitalization cost and 1.1-day increase in LOS in AIS compared to no AF (table 3). LOS and cost in AIS patients with AF also marginally declined over time (table 3).

DISCUSSION In this contemporary analysis of the NIS, we show that AF prevalence in AIS patients in the United States is currently higher than in previous large US studies¹³⁻¹⁵ and that prevalence rates continue to increase. AF prevalence in AIS and TIA

increased with age and over 50% of AIS or TIA patients with comorbid AF were ≥80 years and over 80% were ≥70 years. Prevalence of comorbid AF in AIS was greater among Caucasians and women. Significant heterogeneity in AF prevalence also existed by income, insurance status, region, and hospital characteristics. AF remains associated with increased mortality in AIS but mortality in AIS patients with comorbid AF is on the decline.

AF burden has far-reaching implications on health care planning, research, and allocation of human and economic resources. The high prevalence of comorbid AF in AIS demonstrated in our study highlights the current enormous burden of AF in AIS patients in the United States and rising prevalence indicates that AF remains a growing challenge in AIS prevention in the United States. Because AF-associated strokes are more severe,¹⁶ increasing AF prevalence will require greater investment in health care systems including hospitalization, treatment, and rehabilitation resources, resulting in greater financial burden to society.

Increasing AF prevalence in AIS also indicates that current AIS preventive efforts in patients with AF or current measures to identify AF patients before they develop AIS are far from satisfactory. Innovative AIS preventive strategies are needed, particularly in the elderly ≥80 years, where approximately every 2 in 5 AIS patients had comorbid AF. Some other potential targets for research and therapeutic interventions are the areas of identified disparities highlighted in this study. For example, it is known that women with AF are less likely to receive oral anticoagulation compared to men.^{17,18} Our finding of higher AF prevalence in women with AIS compared to men calls for concerted effort and interventions to address this gap. Socioeconomic

Table 3 Association of atrial fibrillation (AF) with mortality, hospitalization cost, and length of stay in ischemic stroke patients admitted in the United States from 2004 to 2013

	Estimates	95% CI	p
Association of AF compared to no AF with each outcome among all AIS patients			
Mortality, ^a OR	1.93	1.89-1.98	<0.001
Cost, \$ ^b	2310.20	2226.19 to 2394.22	<0.001
Length of stay, d ^b	1.13	1.10-1.16	<0.001
Association of each outcome with unit increase in year when restricted to AIS patients with comorbid AF			
Mortality, ^a OR	0.95	0.94-0.95	<0.001
Cost, \$ ^b	-87.22	-132.53 to -41.91	<0.001
Length of stay, d ^b	-0.19	-0.20 to -0.17	<0.001

Abbreviations: CI = confidence interval; OR = odds ratio.

^aObtained from logistic regression model with mortality as dependent variable, AF as predictor variable, adjusted for age, race, sex, income, insurance status, hospital region, hospital location/teaching status, hospital bed size and hospital stroke volume/year, hospitalization year, and modified Charlson Comorbidity Index after accounting for survey design.

^bObtained from generalized linear model with either cost or length of stay as dependent variable and AF as predictor variable, adjusted for age, race, sex, income, insurance status, hospital region, hospital location/teaching status, hospital bed size and hospital stroke volume/year, hospitalization year, and modified Charlson Comorbidity Index after accounting for survey design.

factors like household income and insurance status may be surrogate markers for health care access and some of the observed differences seen with respect to these factors may represent differences in AF detection resulting from disparity in access to optimal health care, but this needs to be assessed using prospective data.

Although it has been well-established that regional variations in stroke prevalence exist in the United States, with the southern region, the so-called stroke belt, having the highest AIS prevalence,¹⁹ specific data on the regional prevalence of AF in AIS in the United States before now have been sparse. This study provides new data to show that while more AIS hospitalizations with comorbid AF occurred in the South, AF prevalence in AIS is significantly lower in this region compared to AIS in other regions. Reasons for this disparity are unknown and also need to be confirmed in prospective studies.

The increase in AF prevalence seen in our study is likely multifactorial and partly as a result of increased incidence and also due in part to declining AF-related case-fatality rate.^{4,20} Advancing age in addition to increased AF risk factors like obesity and diabetes mellitus in the general US population have led to increased AF incidence,^{20,21} but advances in hospital AF diagnostic approaches and increased AF awareness in the United States have also boosted AF recognition and therefore incidence.²⁰ Declining AF-related mortality in hospitalized US patients implies that more AF patients now live longer and become susceptible to AIS over time.

Our finding of reducing mortality in AIS patients with AF is encouraging and shows that the previously reported trend towards lower mortality in hospitalized AIS patients in the United States has continued.²² However, given the significant difference in mortality in AIS patients with comorbid AF compared to those without AF, more progress is needed to reduce mortality in this subset of AIS patients.

Interestingly, TIAs were once thought to be infrequent in patients with AF.²³ Our study provides novel data demonstrating that AF may be more prevalent in TIA patients than we previously thought but no causal or temporal relationship can be established using our retrospective data.

Our study has several limitations. Although we relied on previously validated codes for AIS and AF, we cannot exclude potential inaccuracies as a result of coding errors. However, given the large size of the NIS, such coding errors are more likely to be random than systemic. As a result of ICD-9 coding limitations, we were also unable to differentiate between first-ever vs recurrent strokes. Some individuals may have had recurrent stroke admissions during our study period and if those with comorbid AF had more

recurrent stroke or TIA hospitalizations, our current prevalence estimate may be an overestimation. We were unable to account for AIS severity using the NIH Stroke Scale, as this metric is not available in the NIS. However, we calculated the CHA₂DS₂-VASc scores and modified CCI as overall measures of comorbidity and took into account comorbid disease status in all our multivariate models. We were also unable to provide information on AF characteristics including new-onset vs chronic AF, paroxysmal vs persistent, or information on specific anticoagulants received before stroke hospitalizations. Holter monitor use during stroke admission was poorly captured in the NIS and so we were unable to analyze trend in Holter monitor use for AF detection over time. A significant proportion of paroxysmal AF is detected as outpatient after AIS admission, so true AF prevalence estimates in AIS patients may be higher than reported in this analysis.

Despite these limitations, our study represents the most current assessment of temporal trends and characteristics of AF in AIS and TIA patients in the United States. Important strengths of our study include the use of clinically diagnosed AIS and TIA cases as opposed to self-reported stroke. The very large sample size of our study with national representation and generalizability to all AIS patients in the United States provide a comprehensive evaluation of the risks, associated determinants, outcomes, and importance of AF for AIS and TIA patients. Our findings should trigger increased efforts to identify the reasons for increased prevalence as the burden of AF-associated AIS and TIA is anticipated to increase even more.

AUTHOR CONTRIBUTIONS

Dr. Otite had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Drs. Otite, Khandelwal, and Malik. Acquisition, analysis, and interpretation of data: Drs. Otite, Khandelwal, Malik, Romano, Sacco, and Chaturvedi. Drafting of the manuscript: Drs. Otite, Khandelwal, and Malik. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Dr. Otite. Administrative, technical, or material support: Drs. Malik, Romano, Chaturvedi, and Sacco. Study supervision: Dr. Malik.

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