

No Decline in the Risk of Stroke Following Incident Atrial Fibrillation Since 2000 in the Community: A Concerning Trend

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Background—While atrial fibrillation is a recognized risk factor for stroke, contemporary data on trends in stroke incidence after the diagnosis of atrial fibrillation are scarce.

Methods and Results—Olmsted County, MN residents with incident atrial fibrillation or atrial flutter (collectively referred to as AF) from 2000 to 2010 were identified. Cox regression determined associations of year of AF diagnosis with ischemic stroke and transient ischemic attack (TIA) occurring through 2013. Among 3247 AF patients, 321 (10%) had an ischemic stroke/TIA over a mean of 4.6 years (incidence rate [95% CI] per 100 person-years: 2.14 [1.91–2.38]). Two hundred thirty-nine (7%) of 3265 AF patients experienced an ischemic stroke (incidence rate: 1.54 [1.35–1.75]). The risk of both outcomes remained unchanged over time after adjusting for demographics and comorbidities (hazard ratio [95% CI] per year of AF diagnosis: 1.00 [0.96–1.04] for ischemic stroke/TIA; 1.01 [0.96–1.06] for ischemic stroke only). In analyses restricted to patients with prescription information, the rates of anticoagulation use did not change over time, reaching 50.8% at 1 year after AF diagnosis. Further adjustment for anticoagulation use did not alter the temporal trends in stroke incidence (hazard ratio [95% CI] per year of AF diagnosis: 1.06 [0.97–1.15] for ischemic stroke/TIA; 1.08 [0.98–1.20] for ischemic stroke only).

Conclusions—Strokes/TIAs are frequent after AF, occurring in 10% of patients after 5 years of follow-up. The occurrence of stroke/TIA did not decline over the last decade, which may be influenced by a leveling off of anticoagulation use. This concerning trend has major public health implications. (*J Am Heart Assoc.* 2016;5:e003408 doi: 10.1161/JAHA.116.003408)

Key Words: atrial fibrillation • ischemic stroke • temporal trends • transient ischemic attack

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in clinical practice, currently affecting between 2.7 and 6.1 million Americans^{1–3} with annual healthcare costs ranging between \$6 and \$26 billion.^{4–6} The outcomes of AF are of major clinical consequence as AF causes substantial morbidity and mortality, including a 5-fold increased risk of stroke⁷ and a nearly 2-fold increased risk of mortality.^{8–10}

Longitudinal data encompassing half a century from the Framingham Heart Study have shown improvements in survival and a decline in the incidence of stroke after AF since 1958.¹¹

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However, recent data suggest that these favorable trends may have leveled off. Indeed, contemporary data indicate that the incidence of AF has stabilized,^{12–14} and although a small increase in survival has been reported among Medicare beneficiaries,¹⁴ community data indicate that survival has not improved in recent times in the community.^{13,15} These data raise the critical question of whether the risk of stroke after AF has continued to improve or has stabilized in contemporary times. While the risk of stroke after AF declined in the Olmsted County, MN community between 1980 and 2000,¹⁶ in a Danish population between 1980 and 2002,¹⁷ and in the general Medicare population between 1992 and 2002,¹⁸ more recent data are lacking on whether these trends have continued or changed. Thus, our objective was to address these gaps in knowledge and provide contemporary data on trends in stroke in a community cohort of patients with incident AF from 2000 to 2010.

Methods

Study Population

This study was conducted in Olmsted County, Minnesota utilizing the resources of the Rochester Epidemiology Project,

a records-linkage system allowing virtually complete capture of healthcare utilization and outcomes in county residents.^{19–22} Olmsted County is relatively isolated from other urban centers and only a few providers, mainly Mayo Clinic, Olmsted Medical Center, and their affiliated hospitals, deliver most health care to local residents. Thus, the retrieval of nearly all healthcare-related events occurring in county residents is possible. This study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. The study was considered minimal risk by both Institutional Review Boards; therefore, the requirement for informed consent was waived. However, we did not review the records of anyone who had not provided authorization for their medical records to be used for research, as per Minnesota statute (Statute 144.335).

Incident AF Cohort

Incident atrial fibrillation or atrial flutter (collectively referred to as AF hereafter) from 2000 to 2010 among adults aged ≥ 18 was identified using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 427.31 and 427.32 from all providers in the Rochester Epidemiology Project and Mayo Clinic ECGs. Events occurring during both inpatient and outpatient encounters were included and all records were manually reviewed to validate the events, as previously described.¹³ AF occurring within 30 days after a coronary artery bypass graft, surgery to repair or replace a heart valve, surgery to repair an atrial septal defect, or other open heart surgery were excluded; among these individuals with postoperative AF, a future episode of AF not associated with a surgical procedure (or occurring more than 30 days after a surgery) was considered incident AF.

Ascertainment of Stroke and Transient Ischemic Attack

Ischemic strokes, transient ischemic attacks (TIA), and hemorrhagic strokes occurring after incident AF through December 31, 2013 were identified using inpatient and outpatient diagnostic codes. Ischemic strokes were identified using ICD-9-CM codes 433 to 434 and 436, TIAs were identified using ICD-9-CM code 435, and hemorrhagic strokes were identified using ICD-9-CM codes 430 to 432. The first event of each type after the incident AF date was ascertained, regardless of whether a patient had a prior stroke or TIA. All events were manually validated by trained nurse abstractors.

The following criteria were required to validate the ischemic strokes²³: (1) acute onset (minutes to hours) of a focal neurologic deficit persisting >24 hours caused by altered circulation to a limited region of the cerebral

hemispheres, brainstem, or cerebellum, and (2) no evidence of intracerebral hemorrhage on computed tomography, magnetic resonance imaging, or autopsy (if available). For TIAs, either of the following criteria were required to validate the event^{24,25}: (1) focal neurological symptoms with abrupt onset and rapid resolution, lasting <24 hours, and caused by focal cerebral ischemia; or (2) transient monocular visual disturbance with abrupt onset and rapid resolution, lasting <24 hours, and caused by retinal ischemia. Intracerebral hemorrhages were validated using the following criteria: (1) acute onset of a focal neurologic deficit associated with some or all of the following: headache, vomiting, altered level of consciousness, signs of meningeal irritation, or blood-stained cerebrospinal fluid; and (2) evidence of parenchymal hemorrhage on computed tomography, magnetic resonance imaging, or autopsy (if available).²³ Finally, for subarachnoid hemorrhages, both of the following criteria were required: (1) abrupt onset of headache, with or without altered consciousness, and with signs of meningeal irritation. A focal deficit may have developed acutely or with a delay of hours or days, and (2) computed tomography, magnetic resonance imaging, or examinations of cerebrospinal fluid showed blood in the subarachnoid space.²³

Clinical Data Collection

Height and weight were abstracted at the time of incident AF, and body mass index was calculated as weight (in kg) divided by height (in meters) squared. Smoking status (current, former, never) was also manually abstracted and those who had smoked within 6 months prior to the incident AF date were considered current smokers. Prior heart failure diagnoses were validated by trained nurse abstractors using the Framingham Criteria.²⁶ The remaining covariates were ascertained electronically and we required 2 occurrences of a code within the 5 years prior to incident AF to rule out false positives due to suspect diagnoses, as described previously.¹³ In addition, the CHA₂DS₂-VASc²⁷ score was calculated. Outpatient prescription data are not routinely available among patients in the Rochester Epidemiology Project prior to 2004; thus, outpatient prescriptions from 2004 through 2013 were obtained from Mayo Clinic and Olmsted Medical Center on the subset of patients with incident AF from 2004 to 2010. Electronic prescriptions from both institutions were retrieved, converted into RxNorm codes, and subsequently grouped using the National Drug File-Reference Terminology.²⁸ All outpatient prescriptions for anticoagulants (National Drug File-Reference Terminology category C8812), which included warfarin, unfractionated heparin, low molecular weight heparin, and novel oral anticoagulants, were obtained in this subset of patients through the end of 2013.

Statistical Analysis

Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC). Characteristics of the cohort at the time of incident AF are presented as means and proportions. Analysis of variance and χ^2 tests were used to compare baseline characteristics across year of AF diagnosis categories (2000–2003, 2004–2007, and 2008–2010). The main analyses focused on the ischemic stroke and TIA outcomes. We pooled ischemic strokes and TIAs together into a composite end point and also completed analyses for ischemic stroke only. For both the ischemic stroke/TIA and ischemic stroke only analyses, the first event after AF was ascertained regardless of whether the patient had a prior cerebrovascular event. However, patients with ischemic strokes or TIAs occurring on the same day as AF were excluded from the analysis. Cumulative incidence curves for each outcome (ischemic stroke/TIA and ischemic stroke only) across year of AF diagnosis categories were constructed treating death as a competing risk,²⁹ adopting the Fine and Gray subdistribution hazard model.³⁰ In addition, cumulative incidence curves were constructed for time to first anticoagulant use across year of AF diagnosis among the subset of the cohort from 2004 to 2010 when prescription data were available.

Cox proportional hazards regression models were used to determine the association of calendar year of AF diagnosis with the risk of ischemic stroke/TIA and ischemic stroke only. For all outcomes, smoothing splines with 4 *df* were constructed to test the linearity assumption and to assess the appropriate functional form of calendar year of AF diagnosis. Year was modeled as a continuous variable and a *P*-value for a time trend was obtained from this model. In addition, for presentation purposes, year of incident AF was categorized and associations were obtained for the following year groups: 2004–2007 and 2008–2010 versus 2000–2003 (reference). All models were adjusted for age, sex, body mass index, current smoking status, and prior diagnoses of hypertension, myocardial infarction, diabetes mellitus, heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, renal disease, and stroke/TIA. In ancillary analyses, we further adjusted for anticoagulant use as a time-dependent variable among the subset of patients with incident AF from 2004 to 2010. For all analyses, age \times year of AF and sex \times year of AF interactions were tested and found to be nonsignificant; thus, results stratified by age or sex are not presented. Finally, Cox regression was used to determine associations of baseline clinical characteristics and comorbidities with the occurrence of each outcome after adjusting for age and sex. The proportional hazards assumption was tested using scaled Schoenfeld residuals and found to be valid for all outcomes.

Because a relatively small number of hemorrhagic strokes were observed (*n*=41), we were underpowered to repeat all

analyses for the hemorrhagic stroke outcome. However, in ancillary analyses, Cox proportional hazards regression models adjusting for age and sex were conducted to assess for changes in the risk of hemorrhagic stroke over time.

Results

Between 2000 and 2010, 3318 patients with incident AF were identified. After excluding patients with missing data (*n*=25) or who experienced an ischemic stroke or TIA on the same day as incident AF (*n*=47), 3247 AF patients remained for the ischemic stroke/TIA analysis and 3265 remained for the ischemic stroke only analysis (Figure 1). The mean (SD) age at time of incident AF was 72.5 (14.7) years and 52% were male (Table 1). The most common comorbidities present at the time of AF diagnosis were hypertension (68%), diabetes mellitus (22%), malignancy (19%), heart failure (17%), and chronic obstructive pulmonary disease (15%). Four hundred thirty-three patients (13%) had a prior ischemic stroke or TIA. The age at AF diagnosis was similar over time; however, a higher proportion of those diagnosed between 2008 and 2010 were male compared to those diagnosed in the earlier time frames. In addition, the prevalence of hypertension, diabetes mellitus, and dementia increased over time while that of chronic obstructive pulmonary disease declined. Finally, the mean CHA₂DS₂-VASc score did not change over time.

Temporal Trends in the Risk of Stroke After AF

Among the 3247 patients in the ischemic stroke/TIA analysis, 321 (10%) developed a subsequent ischemic stroke (*n*=221)

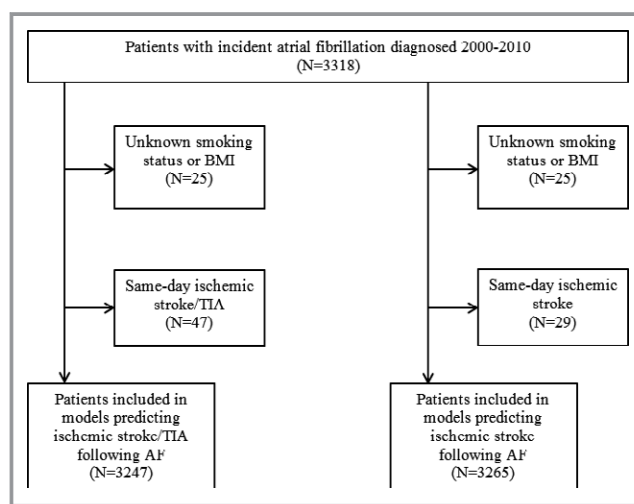


Figure 1. Exclusion criteria and final sample size used in the analysis for each outcome. AF indicates atrial fibrillation; BMI, body mass index; TIA, transient ischemic attack.

Table 1. Baseline Characteristics of the Incident Atrial Fibrillation Patients

	Overall (N=3247)	2000–2003 (N=1067)	2004–2007 (N=1207)	2008–2010 (N=973)	P Value for Trend
Age, y, mean (SD)	72.5 (14.7)	72.7 (14.6)	72.6 (14.8)	72.2 (14.6)	0.44
Age group, n (%)					0.23
<65	822 (25.3)	263 (24.6)	298 (24.7)	261 (26.8)	
65 to 74	739 (22.8)	241 (22.6)	277 (22.9)	221 (22.7)	
≥75	1686 (51.9)	563 (52.8)	632 (52.4)	491 (50.5)	
Male	1684 (51.9)	540 (50.6)	600 (49.7)	544 (55.9)	0.02
White race	3105 (97.2)	1013 (97.7)	1162 (97.3)	930 (96.4)	0.08
Body mass index, kg/m ²					0.08
<25	941 (29.0)	310 (29.1)	375 (31.1)	256 (26.3)	
25 to <30	1059 (32.6)	362 (34.0)	377 (31.2)	320 (32.9)	
≥30	1247 (38.4)	395 (37.0)	455 (37.7)	397 (40.8)	
Smoking status					0.13
Current	337 (10.4)	111 (10.4)	121 (10.0)	105 (10.8)	
Former	1362 (41.9)	434 (40.7)	503 (41.7)	425 (43.7)	
Never	1548 (47.7)	522 (48.9)	583 (48.3)	443 (45.5)	
Hypertension	2207 (68.0)	674 (63.2)	837 (69.4)	696 (71.5)	<0.01
Myocardial infarction	416 (12.8)	146 (13.7)	148 (12.3)	122 (12.5)	0.43
Diabetes mellitus	706 (21.7)	198 (18.6)	259 (21.5)	249 (25.6)	<0.01
COPD	500 (15.4)	208 (19.5)	173 (14.3)	119 (12.2)	<0.01
Peripheral vascular disease	256 (7.9)	74 (6.9)	95 (7.9)	87 (8.9)	0.09
Dementia	127 (3.9)	26 (2.4)	51 (4.2)	50 (5.1)	<0.01
Malignancy	615 (18.9)	221 (20.7)	195 (16.2)	199 (20.5)	0.81
Metastatic solid tumor	148 (4.6)	47 (4.4)	51 (4.2)	50 (5.1)	0.43
Renal disease	211 (6.5)	73 (6.8)	67 (5.6)	71 (7.3)	0.71
Rheumatologic disease	155 (4.8)	52 (4.9)	58 (4.8)	45 (4.6)	0.79
Prior ischemic stroke or TIA	433 (13.3)	141 (13.2)	166 (13.8)	126 (13.0)	0.87
Heart failure	543 (16.7)	191 (17.9)	203 (16.8)	149 (15.3)	0.12
CHA ₂ DS ₂ -VASc score, mean (SD)	3.3 (1.9)	3.2 (2.0)	3.4 (1.9)	3.3 (1.9)	0.59

All results are reported as n (%) unless otherwise specified. COPD indicates chronic obstructive pulmonary disease; TIA, transient ischemic attack.

or TIA (n=100) over a mean follow-up of 4.6 years. For the ischemic stroke only analysis, 239 (7%) ischemic strokes were observed over a mean follow-up of 4.7 years. The incidence rates (95% CI) per 100 person-years were 2.14 (1.91–2.38) and 1.54 (1.35–1.75) for ischemic stroke/TIA and ischemic stroke only, respectively (Table 2). As expected, the rates were higher for those with a CHA₂DS₂-VASc score of 2 or more compared to a CHA₂DS₂-VASc score of 0 to 1.

The risk of developing ischemic stroke/TIA (Figures 2A and 3A) or ischemic stroke only (Figures 2B and 3B) after AF did not differ over time. After adjustment for demographics and comorbidities, the hazard ratio (HR) (95% CI) of ischemic stroke/TIA per year of AF diagnosis was 1.00 (0.96–1.04) ($P=0.80$; Table 3). In addition, no temporal trend was

observed when considering ischemic stroke alone (HR [95% CI] 1.01 [0.96–1.06]; $P=0.73$). In sensitivity analyses including the patients who presented with ischemic stroke/TIA the same day as AF but counting only a subsequent ischemic stroke/TIA after index as an outcome, results were similar (HR [95% CI] per year of AF diagnosis 1.00 [0.96–1.04] for ischemic stroke/TIA and 1.01 [0.97–1.06] for ischemic stroke only).

Interestingly, we also found no evidence of an improvement in survival over time among the 321 patients who developed ischemic stroke/TIA. In fact, after adjustment for age and sex, the HR (95% CI) of death within 30 days of ischemic stroke/TIA was 1.37 (0.99–1.88) per year of AF diagnosis ($P=0.06$), which although nonsignificant, is a

Table 2. Incidence Rates (95% CIs)* for Ischemic Stroke or Transient Ischemic Attack and Ischemic Stroke Only Overall and by Stroke Risk and Warfarin Use Categories

	Ischemic Stroke or Transient Ischemic Attack	Ischemic Stroke Only
Overall rate	2.14 (1.91–2.38)	1.54 (1.35–1.75)
By CHA ₂ DS ₂ -VASc score		
0 to 2	0.82 (0.57–1.15)	0.56 (0.36–0.83)
≥2	2.66 (2.36–2.98)	1.92 (1.68–2.20)
By warfarin use [†]		
No	2.53 (2.12–3.00)	1.97 (1.61–2.38)
Yes	1.66 (1.23–2.18)	1.13 (0.79–1.57)

*Incidence rate (95% CI) per 100 person-years.

[†]Among the subset of atrial fibrillation patients from 2004 to 2010 with available prescription data.

concerning trend that deserves further investigation. Finally, a relatively small number of hemorrhagic strokes were observed in our cohort (n=41). We did not find evidence of a difference in the risk of hemorrhagic stroke over time after adjustment for age and sex (HR [95% CI] per year of AF diagnosis: 0.97 [0.87–1.08]; $P=0.57$).

In analyses restricted to patients diagnosed with AF from 2004 to 2010 when prescription information was available (n=2096 and 2108 for the ischemic stroke/TIA and ischemic stroke only models, respectively), the cumulative incidence (95% CI) of anticoagulation use was 40.0% (37.8% to 42.1%) at 30 days after diagnosis and 50.8% (48.5% to 53.0%) at 1 year after AF diagnosis. A consistent rate of anticoagulation use between 2004 and 2010 was observed (Figure 4). In addition, the mean proportion of time in therapeutic range of warfarin was 50.4%, which did not change over time ($P=0.49$). The incidence rates for ischemic stroke/TIA and ischemic stroke only were lower for those receiving anticoagulation (Table 2). Consistent with our main results, no temporal trend was observed in the risk of ischemic stroke/TIA or ischemic stroke only after further adjustment for anticoagulant use as a time-dependent variable (Table 4), which may be partly explained by the lack of improvement in the use of anticoagulation.

Predictors of Stroke and TIA

Increasing age was a significant predictor of developing ischemic stroke/TIA or ischemic stroke only after adjusting for sex (Figure 5A and 5B). After adjustment for age and sex, having had a prior stroke or TIA was a significant predictor of developing the combined end point of ischemic stroke or TIA. In addition, men exhibited a trend toward a decreased risk of ischemic stroke/TIA and ischemic stroke only, although the

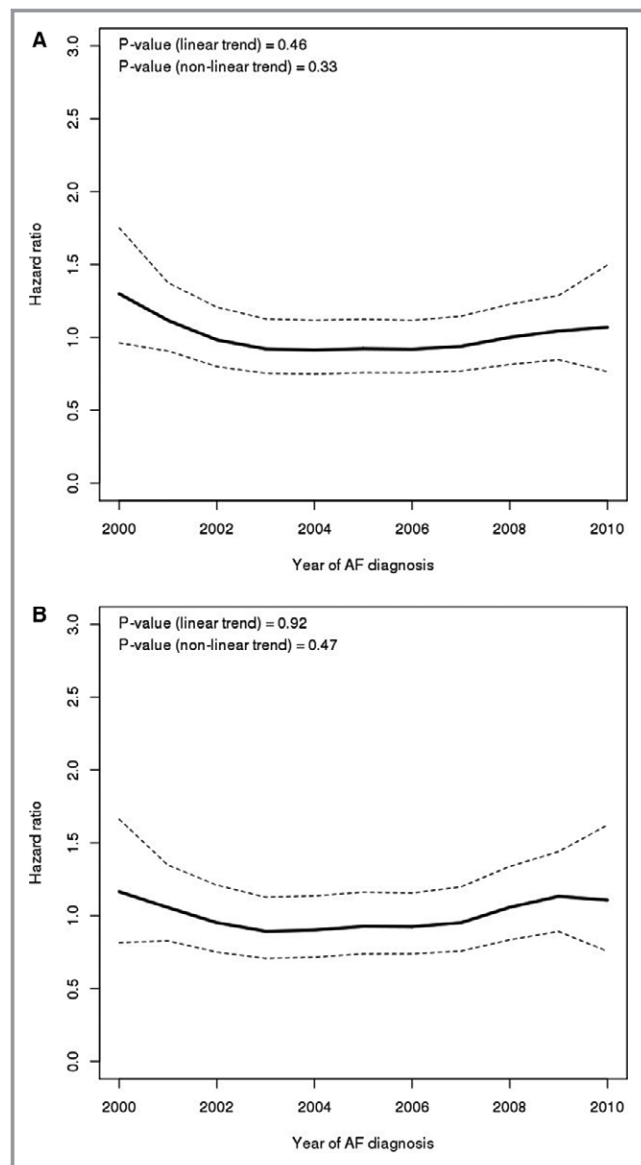


Figure 2. Smoothing splines of the association (hazard ratios [solid line] and 95% CI [dotted lines]) of calendar year of atrial fibrillation diagnosis with the risk of ischemic stroke or transient ischemic attack and ischemic stroke only. (A) Ischemic stroke or transient ischemic attack; (B) ischemic stroke only.

HRs did not reach statistical significance. A trend toward an increased risk of ischemic stroke only was observed for those with hypertension.

Discussion

Previous data from our cohort showed that the incidence of AF has stabilized and survival has not improved over the recent decade.¹³ The present data document that, 5 years after the first ever diagnosis of AF, the risk of experiencing an ischemic stroke or TIA is $\approx 10\%$. Importantly, this risk has remained unchanged over the last decade.

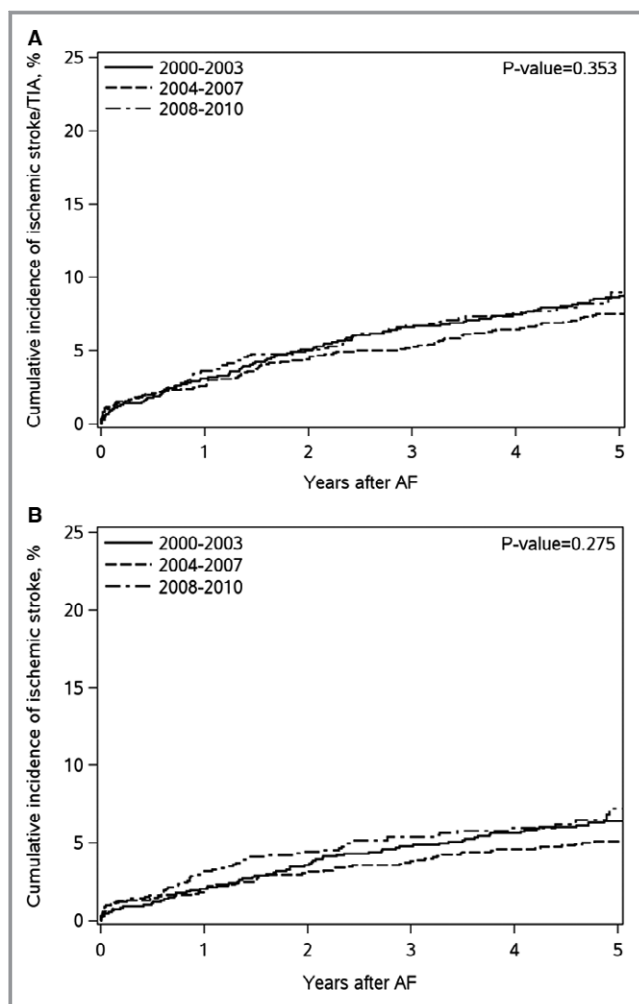


Figure 3. Cumulative incidence of ischemic stroke or transient ischemic attack and ischemic stroke only by year of atrial fibrillation diagnosis. (A) Ischemic stroke or transient ischemic attack; (B) ischemic stroke only. The cumulative incidence curves were adjusted for death as a competing event. AF indicates atrial fibrillation; TIA, transient ischemic attack.

These findings from our contemporary population-based study draw attention to an important public health issue in regard to the underutilization of oral anticoagulation despite extensive evidence-based recommendations of their efficacy. Indeed, despite continued emphasis on improving therapies for patients with AF, the rates of stroke after AF are no longer declining, representing an unfavorable departure from prior community data. In the Framingham Heart Study, the risk of stroke declined 74% over 50 years.¹¹ In Olmsted County between 1980 and 2000, the risk of stroke occurring over a median follow-up of 5.5 years declined 3% per calendar year of AF.¹⁶ In patients with a hospital diagnosis of nonvalvular AF in Denmark, an $\approx 20\%$ decline in the risk of stroke was observed between 1980–1984 and 2000–2002.¹⁷ Finally, in the general Medicare population, the rates of ischemic stroke

Table 3. Hazard Ratios (95% CIs)* for Ischemic Stroke or Transient Ischemic Attack and Ischemic Stroke Only by Year of Atrial Fibrillation Diagnosis

	Ischemic Stroke or Transient Ischemic Attack	Ischemic Stroke Only
N	3247	3265
N events	321	239
Per year	1.00 (0.96–1.04)	1.01 (0.96–1.06)
P time trend	0.80	0.73
By year group		
2000–2003	1.00 (ref)	1.00 (ref)
2004–2007	0.87 (0.67–1.13)	0.92 (0.68–1.25)
2008–2010	1.08 (0.80–1.45)	1.22 (0.86–1.72)

*Models are adjusted for age, sex, body mass index, current smoking status, hypertension, prior myocardial infarction, diabetes mellitus, heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, renal disease, and prior stroke/transient ischemic attack.

in AF patients per 1000 person-years declined from 46.7 to 19.5 between 1992 and 2002.¹⁸

The decline in stroke risk after AF in these aforementioned studies may have been influenced by an increasing trend in the use of warfarin over the same period. Indeed, the rates of warfarin use increased from 9% in 1980–1984 to 30% in 1995–2000 in Olmsted County, MN residents with AF¹⁶ and from 25% in 1992 to 56% in 2002 among Medicare beneficiaries with AF.¹⁸ Hence, the recent leveling off of stroke rates after AF, as observed in our study, is likely influenced by the stabilization in the rates of warfarin use in AF patients over the recent decade. In our community, the rates of anticoagulation reached 40% at 30 days after AF diagnosis and 51% at 1 year after AF diagnosis, and did not

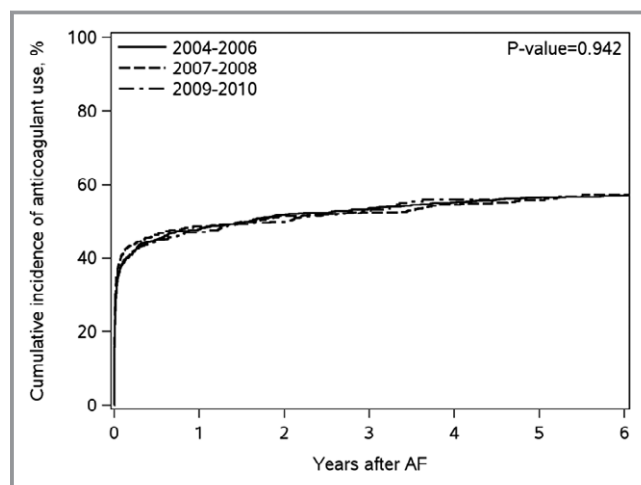


Figure 4. Cumulative incidence of anticoagulant use by year of atrial fibrillation diagnosis. AF indicates atrial fibrillation.

Table 4. Hazard Ratios (95% CI)* for Ischemic Stroke or Transient Ischemic Attack and Ischemic Stroke Only by Year of Atrial Fibrillation Diagnosis in the Subgroup of Patients Diagnosed With Incident Atrial Fibrillation Between 2004 and 2010 With Additional Adjustment for Anticoagulant Use

	Ischemic Stroke or Transient Ischemic Attack	Ischemic Stroke Only
N	2096	2108
N events	185	142
Per year	1.06 (0.97–1.15)	1.08 (0.98–1.20)
P time trend	0.180	0.107
By year group		
2004–2006	1.00 (ref)	1.00 (ref)
2007–2008	1.13 (0.79–1.62)	1.12 (0.73–2.71)
2009–2010	1.21 (0.82–1.79)	1.40 (0.90–2.18)

*Models are adjusted for age, sex, body mass index, current smoking status, hypertension, prior myocardial infarction, diabetes mellitus, heart failure, chronic obstructive pulmonary disease, peripheral vascular disease, renal disease, prior stroke/transient ischemic attack, and anticoagulant use (modeled as a time-dependent variable).

change over the study period. Our rates are consistent with the rates observed in other studies in the United States, with a median of 49.1% of AF patients on warfarin,³¹ underscoring that anticoagulation remains underutilized in AF patients. With the comparative efficacy in terms of stroke prevention and ease of administration of novel oral anticoagulants in comparison to warfarin,³² some improvement in treatment for patients who are not candidates for warfarin is expected, but whether these approaches have a significant impact on further reducing the trend in stroke incidence after AF in the population is yet to be determined. Finally, a small number of AF patients (1.4% in our study) presented with an ischemic stroke/TIA the same day as their AF was diagnosed, which points to the importance of not only optimizing management in patients with known AF, but increased population screening for AF to reduce stroke risk.³³

Increasing age and prior stroke/TIA were found to be predictors of ischemic stroke/TIA in our study. Evidence supports a higher risk of stroke in women compared to men.^{16,17,34} Herein, we observed a similar trend, but sex was not an independent predictor after adjusting for age. Other components of stroke risk prediction tools,^{24,27} such as hypertension, diabetes mellitus and heart failure, were not associated with ischemic stroke/TIA after adjusting for age and sex, although a trend toward an increased risk of ischemic stroke only was observed for hypertension. This apparent discrepancy likely reflects the fact that these risk prediction tools were designed to aid in treatment decisions regarding warfarin in anticoagulation-naïve populations, while our data include all patients in the community with AF, including those being treated with warfarin.

Limitations and Strengths

There are several limitations of our study. First, we may have missed some incident AF events that were miscoded or did not receive a diagnostic code for AF. Second, we did not have sufficient information to characterize the type of AF (paroxysmal, persistent, permanent), thus precluding our ability to determine whether temporal trends differed by type of AF. Third, we may have missed strokes that occurred outside of Olmsted County; however, since the county is relatively isolated and the majority of health care for residents is provided by the few medical centers within the county, we expect this to have been minimal. Finally, although the Olmsted County population is representative of the state of Minnesota and the Midwest region of the United States,²⁰ these findings should be replicated in other populations.

Despite the aforementioned limitations, our study has many strengths. First, our data represent the experience of a community and include all residents with AF in a defined community without restriction on age or insurance provider. Through the Rochester Epidemiology Project records-linkage system, we were able to identify AF and outcomes occurring in both inpatient and outpatient settings from multiple providers in the area, allowing for near complete ascertainment of AF, stroke of all types, and TIA. Finally, our contemporary data have provided convincing evidence that trends in stroke after AF have leveled off and are no longer improving in recent times. From a public health perspective, this is of concern, particularly given the availability of oral anticoagulants of proven efficacy. Importantly, the lack of a decline in stroke is unlikely due to low statistical power. Given the 321 ischemic strokes/TIAs that we observed and assuming categorization of year of AF into 2 distinct time periods, we had 80% power to detect a HR of 1.37 between the 2 time periods assuming $\alpha=0.05$ and a 2-sided test. These estimates are conservative since year of AF was analyzed continuously and, thus, we had adequate power to detect trends of clinical and public health significance.

Conclusions

In the community, the occurrence of ischemic stroke/TIA after diagnosis of AF was common, with 10% of patients experiencing an ischemic stroke/TIA after 5 years of follow-up. The rates of developing ischemic stroke/TIA after AF have not improved since 2000, likely reflecting the stabilization in the rates of anticoagulation. However, future research is warranted to determine whether these trends persist with the adoption of novel oral anticoagulants. These findings underscore the importance of screening for AF and optimizing the management of AF in order to improve outcomes in these patients.

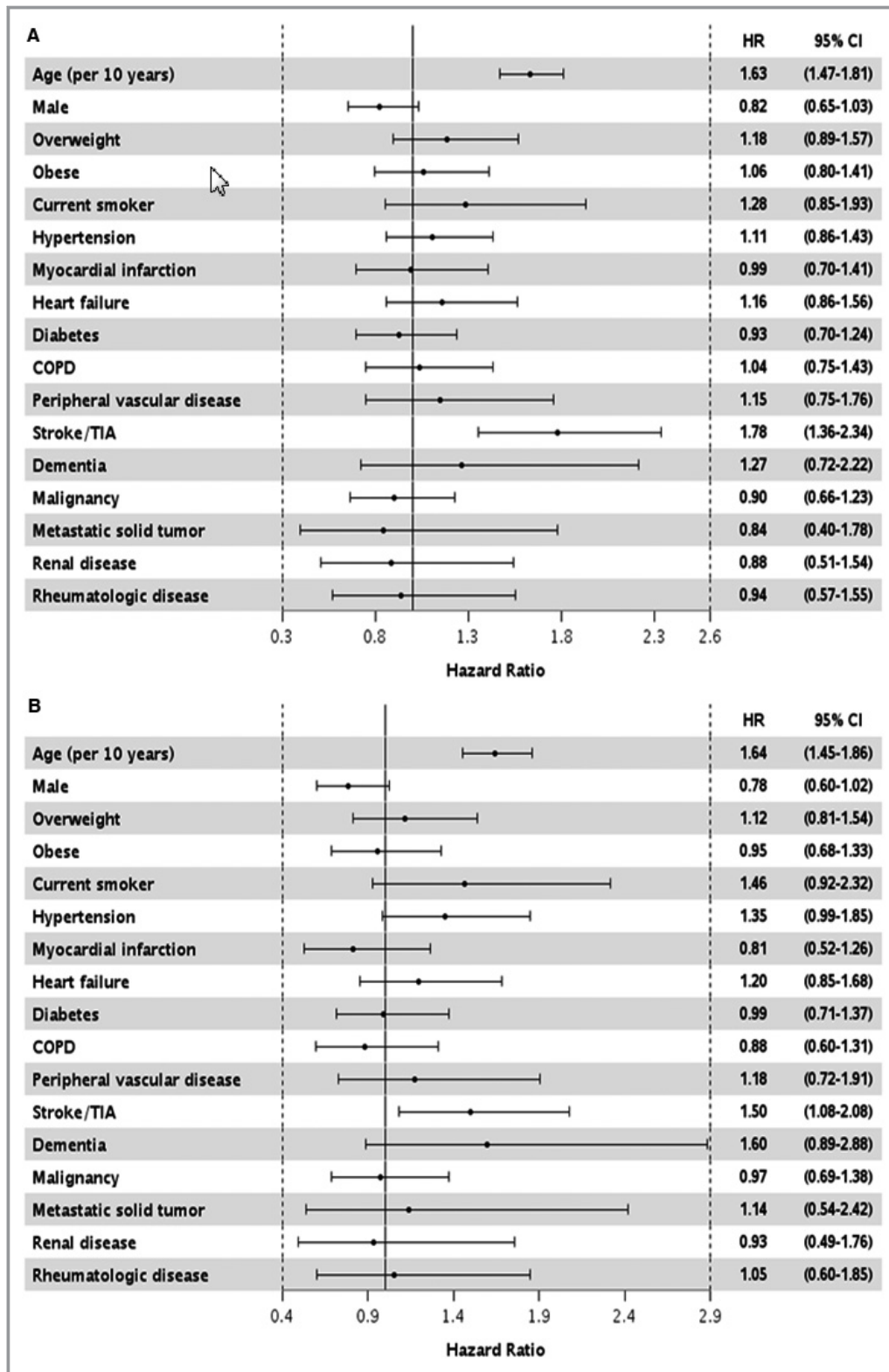


Figure 5. Age- and sex-adjusted predictors of ischemic stroke or transient ischemic attack and ischemic stroke only. (A) ischemic stroke or transient ischemic attack; (B) ischemic stroke only. COPD indicates chronic obstructive pulmonary disease; TIA, transient ischemic attack. The estimate for age is adjusted for sex and the estimate for sex is adjusted for age; all other estimates are adjusted for age and sex. HR indicates hazard ratio.

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Disclosures

None.

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