Atrial Fibrillation and Cognitive Decline–The Role of Subclinical Cerebral Infarcts: The ARIC Study

Lin Y. Chen, MD, MS[*], **Faye L. Lopez, MS, MPH**[†], **Rebecca F. Gottesman, MD, PhD**[‡], **Rachel R. Huxley, DPhil**[§], **Sunil K. Agarwal, MD, PhD**[||], **Laura Loehr, MD, PhD**[#], **Thomas Mosley, PhD**[**], and **Alvaro Alonso, MD, PhD**[†]

[*]Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis, MN [†]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN [‡]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD [§]Queensland Clinical Trials and Biostatistics Center, School of Population Health, University of Queensland [||]Division of Medicine, Johns Hopkins University, Baltimore, USA [#]Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC [**]University of Mississippi School of Medicine, Jackson, Mississippi

Abstract

Background and Purpose—The mechanism underlying the association of atrial fibrillation (AF) with cognitive decline in stroke-free individuals is unclear. We examined the association of incident AF with cognitive decline in stroke-free individuals, stratified by subclinical cerebral infarcts (SCIs) on brain MRI scans.

Methods—We analyzed data from 935 stroke-free participants (mean age±SD, 61.5±4.3 years; 62% women; and 51% black) from 1993–1995 through 2004–2006 in the Atherosclerosis Risk in Communities Study, a biracial community-based prospective cohort study. Cognitive testing (including the Digit Symbol Substitution [DSS] and the Word Fluency [WF] test) was performed in 1993–1995, 1996–1998, and 2004–2006, and brain MRI scans in 1993–1995 and 2004–2006.

Results—During follow-up, there were 48 incident AF events. Incident AF was associated with greater annual average rate of decline in DSS (-0.77; 95% CI, -1.55 to 0.01; $P=0.054$) and WF (-0.80; 95% CI, -1.60 to -0.01; $P=0.048$). Among participants without SCIs on brain MRI scans, incident AF was not associated with cognitive decline. In contrast, incident AF was associated with greater annual average rate of decline in WF (-2.65; 95% CI, -4.26 to -1.03; $P=0.002$) among participants with prevalent SCIs in 1993–1995. Among participants who developed SCIs during follow-up, incident AF was associated with a greater annual average rate of decline in DSS (-1.51; 95% CI, -3.02 to -0.01; $P=0.049$).

Corresponding author: Lin Y. Chen, MD, MS, Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, 420 Delaware Street SE, MMC 508, Minneapolis, MN 55455, USA. Phone: 1-612-625-4401 Fax: 1-612-624-4937 chenx484@umn.edu.

Conclusions—The association of incident AF with cognitive decline in stroke-free individuals can be explained by the presence or development of SCIs, raising the possibility of anticoagulation as a strategy to prevent cognitive decline in AF.

Keywords

Atrial fibrillation; cognitive decline; epidemiology; subclinical cerebral infarcts

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, and its prevalence is increasing over time.[1, 2] AF is associated with an increased risk of stroke,[3] heart failure,[4] and death.[5–7] Evidence is emerging that AF is also associated with another growing public health problem, namely, cognitive impairment or dementia. Earlier studies have shown that the evidence for the association between AF and dementia is strongest in individuals with prevalent stroke; [8–10] in the broader population, the evidence is less clear.[11–13] A meta-analysis reported a 2.4-fold increase in the odds of dementia associated with AF when restricted to patients with stroke.[14] For studies in the broader population, the association between AF and dementia is of borderline significance with substantial heterogeneity in the risk estimates.[14] Later studies, however, provided evidence that AF is associated with cognitive impairment or dementia even in individuals without clinical stroke. Kalantarian et al. reported in a meta-analysis that AF was associated with an increased risk of cognitive impairment and dementia, with or without a history of clinical stroke.[15] In addition, recent reports from the Cardiovascular Health Study[16] and ONTARGET and TRANSCEND studies[17] indicated that in the absence of clinical stroke, participants with AF experienced faster cognitive decline than those without AF. Although compelling, the mechanism underlying the association between AF and cognitive decline or dementia in the absence of clinical stroke was not elucidated in the aforementioned studies. Understanding the mechanism underlying the association between AF and cognitive decline or dementia in stroke-free individuals is critical in informing prevention strategies for cognitive decline in these individuals.

Based on a previous report that 14.7% of patients with AF had silent cerebral infarcts on cranial CT scans,[18] we hypothesized that incident AF is associated with greater cognitive decline in individuals without clinical stroke via SCIs. To test our hypothesis, we evaluated in a stroke-free population the association between incident AF and rate of cognitive decline, stratified by the presence or absence of subclinical cerebral infarcts (SCIs) on brain MRI scans. We tested our hypothesis in the Atherosclerosis Risk in Communities (ARIC) Study, a large USA community-based cohort study of cardiovascular disease.

METHODS

Study Population

The ARIC cohort is a biracial population-based sample from 4 communities in North Carolina, Mississippi, Minnesota, and Maryland, consisting of 15792 men and women, and 45–64 years of age at baseline or visit 1 (1987–1989).[19] After the visit 1 examination, there were 3 additional exams: visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998).

Cognitive assessments were performed in the entire ARIC cohort at visit 2 (n=14128) and visit 4 (n=11093). Of the 6715 participants who returned for ARIC visit 3 (1993–1995) at 2 ARIC Field Centers (i.e., Forsyth County, NC, and Jackson, MS), 2891 participants aged 55 years and older were invited for brain MRI scan and cognitive assessment (Figure I, online supplement). Usual safety exclusion criteria for MRI excluded 2% of women and 6% of men; brain MRI studies and cognitive assessments were performed in 1920 and 2053 participants, respectively, at visit 3. All participants with MRI scanning at visit 3 were invited to undergo another brain MRI scan and cognitive assessment in 2004–2006; 1129 and 1097 participants completed brain MRI scan and cognitive assessment, respectively, in 2004–2006 (Figure I, online supplement). We included in our analysis cohort, participants who had cognitive assessments performed at visit 3, visit 4, 2004–2006, and brain MRI studies at visit 3 and 2004–2006 (n=1024). Therefore, visit 3 (1993–1995) was the baseline of our analysis and the follow-up was through 2004–2006. After exclusions, the final analysis cohort comprised 935 participants. Figure II in the online supplement shows the exclusion criteria and the final number of participants enrolled in the analysis cohort.

The ARIC Study protocol was approved by the institutional review board of each participating center and informed consent was obtained from each study participant.

Ascertainment of Atrial Fibrillation

AF diagnoses were obtained from ECGs at 4 study visits and hospital discharge records through December 31, 2009.[20] Hospitalizations in ARIC are identified by participant or proxy report in the annual follow-up and by surveillance of local hospital discharge lists. All ECG recordings automatically coded as AF were visually rechecked by a cardiologist to confirm the diagnosis.[21] A trained abstractor obtained and recorded all International Classification of Diseases, Ninth Revision (ICD-9) hospital discharge diagnoses from each hospitalization. AF was defined as the presence of ICD-9 code 427.31 or 427.32 in the discharge codes. By physician review of 125 discharge summaries with ICD codes indicating possible AF, we confirmed the presence of AF in approximately 90%.[20]

Ascertainment of Ischemic Stroke

Prevalent stroke at ARIC visit 1 was defined as a self-reported history of physician-diagnosed stroke. To identify incident stroke, cohort participants were followed over time through annual telephone interviews, triennial field center examinations, surveillance of the ARIC community hospitals for all cohort members' hospitalizations, and the review of death certificates, physician questionnaires, coroner/medical examiner reports, and informant interviews. Hospital reports were reviewed for evidence of acute stroke if the discharge diagnosis included a cerebrovascular disease code (ICD-9 codes 430 to 438), if a cerebrovascular procedure was mentioned in the summary, or if the CT or MR report showed evidence of cerebrovascular disease. Medical records for potential stroke events were forwarded to a single nurse abstractor at a central ARIC office who abstracted each record for number, type, and severity of neurological deficits and supporting angiographic, CT, MRI, spinal tap, or autopsy evidence. ARIC adapted National Survey of Stroke criteria for its stroke definition.[22] A computerized algorithm and physician reviewer independently confirmed the diagnosis of stroke with disagreements adjudicated by a second physician

reviewer. Stroke cases were further classified as definite versus probable and into further subtypes as embolic versus thrombotic stroke.[23] For this study, incident ischemic stroke included definite or probable ischemic strokes (embolic or thrombotic).

Cognitive Testing

Cognitive assessments, baseline performance, and longitudinal characteristics of the cognitive assessment battery have been previously reported.[24, 25] This battery included the Delayed Word Recall (DWR) Test, the Digit Symbol Substitution (DSS) Subtest of the Wechsler Memory Scale-Revised, and the first-letter Word Fluency (WF) Test. Details of the tests are presented in the Supplemental Methods in the online supplement.

Brain MRI

The ARIC Study MRI screening protocol and image analyses have been previously described.[26] Briefly, 1.5 T magnetic resonance scanners (GE and Picker) were used. Axial images were angled to be parallel to the anterior commissure–posterior commissure line. The digital scan images, including SD/T2 weighted (3000, 30–100, TR, and TE) and T1 weighted images, were evaluated at the MRI Reading Center on a Vortech Personal Display System (PDS-4) workstation. The image evaluation was conducted by trained and certified MRI readers. SCIs were defined as focal, non-mass lesions 3 mm that were bright on T2 and proton density, and dark on T1 images. All scans were subjected to double-reads for infarct scoring.

Covariates

Definitions of covariates are presented in the Supplemental Methods in the online supplement.

Statistical Analysis

We report means with standard deviations (SDs) or medians and interquartile ranges (IQR) for continuous variables and counts with percentages for categorical variables.

To test the association between AF and cognitive decline rate, we used mixed-effects linear models (PROC MIXED). The models consisted of AF status, time of follow-up (in years), and a term for the interaction of AF x time. Participants who developed incident stroke after visit 3 were excluded from the analysis. Model 1 was adjusted for age, sex, race, and interaction terms: age x time, sex x time, and race x time. Model 2 was additionally adjusted for field center, educational level (<high school, completed high school, some college), and time-varying smoking status (current, not current), body mass index, hypertension, diabetes, coronary heart disease (CHD), and heart failure. The coefficient for time estimates the average annual rate of change in the cognitive test score, and the coefficient for the interaction term (AF x time) estimates the difference in average annual rate of change associated with the presence of AF.

To determine whether the association between AF and cognitive decline is mediated by SCIs, we performed 3 additional analyses. First, we repeated the analysis in participants who did not have SCIs at both visit 3 and in 2004–2006. Second, we evaluated the association

between incident AF and cognitive decline rate in participants with prevalent SCIs at visit 3. Third, we evaluated the association between incident AF and cognitive decline rate in participants without SCIs at visit 3 and who developed SCIs by 2004–2006.

Finally, to further evaluate whether SCIs mediate the cognitive decline associated with AF, we conducted a secondary analysis by assessing the association of prevalent or incident SCIs with change in cognitive scores, stratified by presence or absence of incident AF.

Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). All *P* values reported were 2-sided, and statistical significance threshold was chosen as 5%.

RESULTS

Study Population

The analysis cohort consisted of 935 participants (mean age, 61.5 [SD, 4.3] years at baseline; 62.0% women; 50.7% black). During a median (IQR) follow-up of 10.6 (9.8–11.2) years, 48 participants developed AF. Compared with participants who did not develop AF, there were more men and whites among participants who developed AF. Participants who developed AF were also older and had higher prevalence of current smoking, hypertension, and CHD. Table 1 shows the baseline characteristics of study participants.

Table I in the online supplement stratifies participants with AF by CHA_2DS_2–VASc score and describes the proportion of participants with AF who were anticoagulated. Of 48 participants with AF, 28 (58.3%) had CHA_2DS_2–VASc score 2, meeting definite criteria for anticoagulation. The rate of anticoagulation, however, was very low even among participants with CHA_2DS_2–VASc score 2. Of 48 participants with incident AF, 20 (41.7%) had a $CHADS_2$ score of 0, 23 (47.9%) had a score of 1, and 5 (10.4%) had a score of 2. Therefore, based on $CHADS_2$ score, 89.6% of participants had $CHADS_2$ score <2 and would not have met definite criteria for anticoagulation.

Atrial Fibrillation and Cognitive Decline

Table II in the online supplement shows the summary cognitive test scores of study participants at visit 3, visit 4, and 2004–2006. Participants who developed AF had greater annual average rate of decline in DSS (–0.77; 95% CI, –1.55 to 0.01; *P*=0.054) and WF (–0.80; 95% CI, –1.60 to –0.01; *P* =0.048) than those who did not develop AF (Table 2). Incident AF was not associated with a greater rate of decline in DWR.

To evaluate whether or not incident AF is associated with greater cognitive decline in the absence of SCIs, we repeated the analysis restricting to participants who did not have SCIs at both visit 3 and 2004–2006. In this subset comprising 699 participants of whom 29 developed AF, incident AF was not associated with decline in all 3 cognitive test scores (Table 3).

Next, we evaluated the association of incident AF and cognitive decline in participants who had prevalent SCIs at visit 3. There were 67 participants in this subset of whom 3 developed AF. In this subset, compared with participants who did not develop AF, participants who

developed AF had greater annual average rate of decline in WF (−2.65; 95% CI, −4.26 to −1.03; *P* =0.002) but not in DWR and DSS (Table 4).

Finally, we evaluated the association of incident AF and cognitive decline in participants who did not have SCIs at visit 3 but developed them by 2004–2006. In this subset comprising 169 individuals, participants who developed AF (n=16) had greater annual average rate of decline in DSS (−1.51; 95% CI, −3.02 to −0.01; *P*=0.049) than those who did not develop AF. Incident AF was not associated with decline in DWR or WF (Table 5).

Risk Factors and Impact of Subclinical Cerebral Infarcts

Table III in the online supplement shows selected baseline characteristics (at Visit 3) of participants without prevalent or incident SCIs vs. those with prevalent or incident SCIs. The distribution of stroke risk factors was not significantly different between the 2 groups with the exception of hypertension and AF; the prevalence of hypertension and AF incidence were significantly higher among participants with prevalent or incident SCIs. Further, in participants with incident AF, the proportion who developed SCIs was 16 of 48 (33.3%); this proportion was almost double that in participants without incident AF, 153 of 887 (17.3%). Table IV in the online supplement shows the number (%) of participants with SCIs on their brain MRI scans at ARIC visit 3 and 2004–2006. Collectively, the data suggest that AF is an important risk factor for SCIs.

To further evaluate whether SCIs mediate the cognitive decline associated with AF, we conducted a secondary analysis. In this secondary analysis, we assessed the association of prevalent or incident SCIs with change in cognitive scores, stratified by presence or absence of incident AF. We found that compared with absence of prevalent or incident SCIs, presence of prevalent or incident SCIs was significantly associated with greater decline in DSS, even in participants without AF (Table 6). This observation suggests that it is not AF *per se*, but rather SCIs that are related to cognitive decline.

DISCUSSION

In a large biracial population-based cohort study that comprised middle-aged individuals, we observed that participants without clinical stroke who developed AF had greater cognitive decline compared with participants who did not develop AF. However, this association was true only in participants who had prevalent SCIs or who developed SCIs during follow-up. In individuals without prevalent SCIs or who did not develop SCIs during follow-up, incident AF was not associated with cognitive decline. Further, prevalent or incident SCI was significantly associated with greater cognitive decline, even in the absence of AF. Collectively, our observations suggest that the association between incident AF and cognitive decline is mediated by the presence or development of SCIs.

A recent meta-analysis of 21 studies has provided compelling evidence for an association between AF and cognitive impairment or dementia.[15] AF was significantly associated with an increased risk of cognitive impairment in patients with first-ever or recurrent stroke (relative risk [RR], 2.70; 95% CI, 1.82–4.00) and in a broader population including patients with or without a history of stroke (RR, 1.40; 95% CI, 1.19–1.64). Of note, among studies

that excluded patients with prevalent stroke or adjusted the risk estimates for prevalent stroke, AF was also significantly associated with an increased risk of cognitive impairment (RR, 1.34; 95% CI, 1.13–1.58). However, the possibility of silent stroke or SCIs as the mechanism underlying the association in patients without clinical stroke cannot be excluded.

The findings of our study are consistent with the recent meta-analysis above[15] and recent reports from the Cardiovascular Health Study,[16] ONTARGET and TRANSCEND studies,[17] and provide further evidence that incident AF is associated with dementia or cognitive decline in individuals without stroke. The VA Stroke Prevention in Nonrheumatic AF Investigators reported that 14.7% of patients with AF had silent cerebral infarcts on cranial CT scans.[18] Further, from a recent case-control study by Gaita et al., silent cerebral ischemia was reported to be more prevalent in patients with AF than in controls, and cognitive performance was worse in patients with AF than in controls.[27] However, the study did not demonstrate that the worse cognitive performance in patients with AF was mediated by silent cerebral ischemia. Based on the findings of the VA study and the study by Gaita et al., we hypothesized that incident AF may be associated with greater cognitive decline in individuals without clinically manifested stroke via SCIs. To test our hypothesis, we performed additional analyses stratified by the presence or absence of SCIs as determined by brain MRI scans. In individuals without SCIs, incident AF was not associated with cognitive decline. By way of contrast, in participants with prevalent SCIs or who developed SCIs during follow-up, incident AF was related to greater rate of cognitive decline. Thus, the association between AF and cognitive decline can be explained by the presence or development of SCIs.

The majority of SCIs in our study were likely deeply located in the deep nuclear region and deep cerebral white matter.[28] Nevertheless, these lesions could still be related to AF. The VA Stroke Prevention in Nonrheumatic AF Investigators reported in a study of 516 patients with AF who underwent cranial CT scans that 46 of 76 (61%) patients with SCIs had lesions that were small and located in the deep hemispheric areas that are typically classified as lacunar infarcts.[18] Therefore, SCIs that are related to AF are not exclusively located superficially; they can also be deeply located.

Cognitive decline associated with AF was reflected in a greater annual average change in DSS and WF, but not DWR. The pattern of cognitive decline is worth noting. In general, DWR is a test of recent memory, DSS is a test of attention, and WF is a test of executive function. In participants with prevalent SCIs, incident AF was associated with a greater decline in executive function (WF), whereas in participants who developed SCIs during follow-up, incident AF was associated with a greater decline in attention (DSS). The ARIC study had previously reported that over a 14-year follow-up (visit 2 through 2004–2006), diabetes was associated with a decline in DSS and WF, hypertension was associated with a decline in WF, and systolic blood pressure was related to a decline in DSS.[29] The *APOE ε4* genotype–most strongly associated with the risk of Alzheimer's disease–was associated with declining performance in DWR.[29] These patterns are consistent with a model of pathoanatomic relationships where lacunar infarcts[30] and vascular risk factors[31, 32] are associated with attentional and executive function deficits, whereas Alzheimer's disease-related risk is associated with decline in memory functioning.[33, 34] These data suggest that

although SCI may be the principal mechanism that mediates cognitive decline associated with AF, the possible contribution of other shared risk factors (e.g., hypertension) cannot be entirely excluded.

The strengths of this study include the long follow-up, inclusion of black participants, and extensive measuremelet of covariates. However, several limitations should be noted. First, incident AF was identified mostly from hospitalization discharges and we could have missed asymptomatic AF or AF managed exclusively in an outpatient setting. However, we and others have previously shown that the validity of AF ascertainment using hospitalizations is acceptable,[20, 35] that incidence rates of AF in ARIC are consistent with other population-based studies,[20, 35] and that the associations between genetic variants in the chromosome 4q25 locus and AF–extremely specific for AF risk–in ARIC are similar to other studies with a more rigorous ascertainment of AF.[36] Second, we defined SCIs as focal, non-mass lesions 3 mm that were bright on T2 and proton density, and dark on T1 images. Therefore, participants with SCIs <3 mm might have been misclassified. Third, ARIC participants who failed to complete the 11 years of observation (ARIC visit 3 through 2004–2006) because of death, an inability to undergo MRI, or refusal had greater burdens of disease (e.g., diabetes, hypertension), lower baseline cognitive test scores and worse baseline MRI findings than those who completed follow-up. Therefore, participants who completed the longitudinal assessments described here comprised the healthier subset of the original cohort. Because of the loss to follow-up of participants with more disease burden and cognitive impairment at baseline, we may have underestimated the degree of cognitive decline during the 11 years of observation. However, we do not expect this loss to follow-up to introduce a substantial bias on the assessment of the association between AF and cognitive decline because in all our analyses we have adjusted for determinants of participation in the follow-up exams (e.g., diabetes, hypertension, coronary heart disease, and others). Fourth, since we are unable to classify AF type (paroxysmal, persistent, or permanent AF) accurately in the ARIC study, we did not assess the relationship between AF type and cognitive decline or SCIs. Finally, information on warfarin use from the study visits and annual follow-up phone calls may not be complete.

Our findings have important clinical and public health implications. Since the majority of our participants with AF do not meet criteria for anticoagulation (based on $CHADS_2$) to prevent stroke, our findings raise 2 questions: First, should patients with AF be anticoagulated to prevent cognitive decline, even if they don't meet criteria for anticoagulation to prevent stroke? Second, should persons with SCIs, irrespective of AF, be prescribed antiplatelet agents or anticoagulants to prevent cognitive decline? In addition, since more participants with AF met definite criteria for anticoagulation based on CHA_2DS_2–VASc (58.3% of participants with AF had CHA_2DS_2–VASc score 2) than $CHADS_2$ (10.4% of participants with AF had a $CHADS_2$ score of 2), the CHA_2DS_2–VASc score may be a more appropriate tool for ascertaining need for anticoagulation in AF. These questions will need to be addressed in other prospective studies and clinical trials.

In conclusion, in a large biracial population based-cohort study of middle-aged individuals without stroke, incident AF is independently associated with greater cognitive decline. This association can be explained by the presence or development of SCIs. Presently,

anticoagulation is indicated in most patients with AF to prevent thromboembolic stroke.[37] In AF patients without risk factors for stroke (and hence without current indication for anticoagulation), further research is needed to evaluate whether anticoagulation would be beneficial in preventing cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline Characteristics by Atrial Fibrillation Status, Atherosclerosis Risk in Communities Study, 1993–2006

		Incident AF through 2006	
	Total sample (n=935)	No (n=887)	Yes (n=48)
Age, mean (SD), years	61.5 (4.3)	61.4 (4.3)	63.2 (4.3)
Female	62.0	62.5	54.2
Black race	50.7	51.1	43.8
Educational level			
<High school	19.3	18.7	29.2
Completed high school	33.4	33.6	29.2
Some college	47.4	47.7	41.7
Cigarette smoking			
Current	13.2	12.5	27.1
Former	38.3	38.2	39.6
Never	49.5	49.3	33.3
Body mass index, mean (SD), kg/m^2	27.8 (4.8)	27.8 (4.8)	27.8 (5.5)
Diabetes	13.3	13.2	14.6
Hypertension	42.9	42.3	54.2
Coronary heart disease	2.7	2.3	10.4
Heart failure	0.11	0.11	0

Data are presented as percentage of column unless otherwise stated.

AF, atrial fibrillation; SD, standard deviation

Table 2

Change in Cognitive Test Scores by Atrial Fibrillation Status, Atherosclerosis Risk in Communities Study, 1993–2006

		AF x Time		
		No (n=887)	Yes (n=48)	*P* Value
Delayed Word Recall				
	Model 1[*]	[Referent]	0.07 (−0.09 to 0.24)[‡]	0.38
	Model 2[†]	[Referent]	0.08 (−0.09 to 0.24)[‡]	0.35
Digit Symbol Substitution				
	Model 1[*]	[Referent]	−0.77 (−1.55 to 0.01)[‡]	0.05
	Model 2[†]	[Referent]	−0.77 (−1.55 to 0.01)[‡]	0.05
Word Frequency				
	Model 1[*]	[Referent]	−0.78 (−1.58 to 0.01)[‡]	0.06
	Model 2[†]	[Referent]	−0.80 (−1.60 to −0.01)[‡]	0.05

AF, atrial fibrillation.

[*] Mixed-effects linear model adjusted for age, sex, race, and interactions of age x time, sex x time, and race x time.

[†] Mixed-effects linear model additionally adjusted for field center, educational level, and time-varying smoking status, body mass index, hypertension, diabetes, coronary heart disease, and heart failure.

[‡] Difference (95% CI) in annual average rate of change in cognitive test scores associated with AF.

Table 3

Change in Cognitive Test Scores by Atrial Fibrillation Status in Participants Without Subclinical Cerebral Infarcts at Baseline (Visit 3) and During Follow-Up, Atherosclerosis Risk in Communities Study, 1993–2006

		AF x Time		
		No (n=670)	Yes (n=29)	*P* Value
Delayed Word Recall				
	Model 1[*]	[Referent]	0.21 (−0.02 to 0.44)[‡]	0.07
	Model 2[†]	[Referent]	0.20 (−0.03 to 0.43)[‡]	0.09
Digit Symbol Substitution				
	Model 1[*]	[Referent]	−0.23 (−1.30 to 0.84)[‡]	0.67
	Model 2[†]	[Referent]	−0.37 (−1.44 to 0.69)[‡]	0.49
Word Frequency				
	Model 1[*]	[Referent]	0.25 (−0.90 to 1.40)[‡]	0.67
	Model 2[†]	[Referent]	0.10 (−1.04 to 1.25)[‡]	0.86

AF, atrial fibrillation.

[*] Mixed-effects linear model adjusted for age, sex, race, and interactions of age x time, sex x time, and race x time.

[†] Mixed-effects linear model additionally adjusted for field center, educational level, and time-varying smoking status, body mass index, hypertension, diabetes, coronary heart disease, and heart failure.

[‡] Difference (95% CI) in annual average rate of change in cognitive test scores associated with AF.

Table 4

Change in Cognitive Test Scores by Atrial Fibrillation Status in Participants With Subclinical Cerebral Infarcts at Baseline (Visit 3), Brain Ancillary Atherosclerosis Risk in Communities Study, 1993–2006

		AF x Time		
		No (n=64)	Yes (n=3)	*P* Value
Delayed Word Recall				
	Model 1[*]	[Referent]	−0.10 (−0.50 to 0.31)[‡]	0.63
	Model 2[†]	[Referent]	−0.11 (−0.53 to 0.30)[‡]	0.59
Digit Symbol Substitution				
	Model 1[*]	[Referent]	−1.03 (−3.28 to 1.23)[‡]	0.37
	Model 2[†]	[Referent]	−0.97 (−3.21 to 1.27)[‡]	0.39
Word Frequency				
	Model 1[*]	[Referent]	−2.69 (−4.29 to −1.08)[‡]	0.001
	Model 2[†]	[Referent]	−2.65 (−4.26 to −1.03)[‡]	0.002

AF, atrial fibrillation.

[*] Mixed-effects linear model adjusted for age, sex, race, and interactions of age x time, sex x time, and race x time.

[†] Mixed-effects linear model additionally adjusted for field center, educational level, and time-varying smoking status, body mass index, hypertension, diabetes, coronary heart disease, and heart failure.

[‡] Difference (95% CI) in annual average rate of change in cognitive test scores associated with AF.

Table 5

Change in Cognitive Test Scores by Atrial Fibrillation Status in Participants With Development of Subclinical Cerebral Infarcts During Follow-Up, Atherosclerosis Risk in Communities Study, 1993–2006

		AF x Time		
		No (n=153)	Yes (n=16)	*P* Value
Delayed Word Recall				
	Model 1[*]	[Referent]	0.01 (−0.30 to 0.32)[‡]	0.96
	Model 2[†]	[Referent]	0.03 (−0.28 to 0.35)[‡]	0.83
Digit Symbol Substitution				
	Model 1[*]	[Referent]	−1.59 (−3.07 to −0.10)[‡]	0.04
	Model 2[†]	[Referent]	−1.51 (−3.02 to −0.01)[‡]	0.05
Word Frequency				
	Model 1[*]	[Referent]	−1.04 (−2.48 to 0.39)[‡]	0.15
	Model 2[†]	[Referent]	−1.04 (−2.50 to 0.42)[‡]	0.16

AF, atrial fibrillation.

[*] Mixed-effects linear model adjusted for age, sex, race, and interactions of age x time, sex x time, and race x time.

[†] Mixed-effects linear model additionally adjusted for field center, educational level, and time-varying smoking status, body mass index, hypertension, diabetes, coronary heart disease, and heart failure.

[‡] Difference (95% CI) in annual average rate of change in cognitive test scores associated with AF.

Table 6

Change in Cognitive Test Scores by Subclinical Cerebral Infarct Status Stratified by Atrial Fibrillation, Atherosclerosis Risk in Communities Study, 1993–2006

Prevalent or incident SCI		SCI x Time		
No incident AF		No (n=670)	Yes (n=217)	P Value
Delayed word recall	Model 1[*]	[Referent]	−0.004 (−0.03 to 0.02)[†]	0.76
Digit symbol substitution	Model 1[*]	[Referent]	−0.14 (−0.24 to −0.03)[†]	0.008
Word frequency	Model 1[*]	[Referent]	0.02 (−0.08 to 0.12)[†]	0.71
Incident AF		No (n=29)	Yes (n=19)	
Delayed word recall	Model 1[*]	[Referent]	−0.07 (−0.15 to 0.01)[†]	0.09
Digit symbol substitution	Model 1[*]	[Referent]	−0.13 (−0.54 to 0.27)[†]	0.52
Word frequency	Model 1[*]	[Referent]	−0.25 (−0.71 to 0.21)[†]	0.29

AF, atrial fibrillation; SCI, subclinical cerebral infarct

[*] Mixed-effects linear model adjusted for age, sex, race, and interactions of age x time, sex x time, and race x time.

[†] Difference (95% CI) in annual average rate of change in cognitive test scores associated with SCI.