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Persistent but not Paroxysmal Atrial Fibrillation is Independently Associated with Lower Cognitive Function: The Atherosclerosis Risk in Communities (ARIC) Study

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The association of atrial fibrillation (AF) with an increased risk of cognitive impairment or dementia is independent of clinical stroke (1) and may be mediated by subclinical cerebral infarcts (SCIs) (2). However, little is known about whether or not AF burden—the percentage of time a person is in AF—is related to cognitive function. Moreover, if such a relationship exists, whether it is mediated by clinical stroke or SCIs is unknown. We hypothesized that higher AF burden will be independently associated with lower cognitive function after adjustment for clinical stroke but this association will be attenuated after adjustment for SCIs. We tested our hypothesis in a sample of participants from the Atherosclerosis Risk in Communities (ARIC) study, a large USA community-based cohort.

After the baseline examination (1987–1989), ARIC participants had 4 additional exams. The last exam (visit 5) in 2011–2013 was attended by 6,538 participants, with extensive cognitive tests conducted as part of the ARIC Neurocognitive Study (ARIC-NCS), an ancillary study to the main ARIC study (3). Additionally, a subset of ARIC visit 5 exam participants (n=1,906) was selected to undergo brain magnetic resonance imaging (MRI) scans. In July 2013–March 2014, 325 participants at 2 field centers who presented for their

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There are no relationships with industry

brain MRI scans at visit 5/NCS exam wore the Zio®Patch, a leadless electrocardiogram monitor (iRhythm Technologies, Inc, San Francisco, CA) (4).

AF was defined as an irregularly irregular rhythm with absent P waves lasting ≥30 seconds. AF burden was defined as the percent of analyzable recording time that a participant was in AF. Participants were administered a battery of neuropsychological tests covering different cognitive domains (Table). SCIs on brain MRI scans were defined as focal, non-mass lesions ≥3 mm that were bright on T2 and proton density and dark on T1 images.

The mean age (standard deviation) of participants in the study was 76.9 (5.2) years and 172 (52.9%) participants were women. All, except for 6 participants, were white. Twenty-six (8%) participants were found to have AF by heart rhythm monitoring and 15 (4.6%) had a prior ischemic stroke. The Zio®Patch performed very well in this study: the median (interquartile range) wear time and analyzable time were 13.9 (13.3–14.0) and 13.6 (12.8–13.8) days, respectively, out of a possible maximum of 14 days. The distribution of AF burden was bimodal: 14 participants with AF had AF burden ranging from 1–6% and 12 had AF burden at 100%.

Presence of AF *per se* was not significantly associated with lower cognitive scores after adjustment for clinical stroke. By contrast, AF burden of 100% was significantly associated with lower cognitive scores: After adjustment for risk factors in Model 2, compared to participants without AF, those with AF burden of 100% had lower Digit Span Backwards (DSB), Trail Making Test (TMT) b, and Animal Naming (AN) *Z*-scores (Table). Further, the associations of 100% AF burden with lower DSB, TMTb, and AN *Z*-scores remained significant even after adjustment for prevalent ischemic stroke and SCIs. By contrast, participants with AF burden 1–6% did not have lower cognitive test scores than those without AF (p values for difference based on AF burden for DSB, TMTb, and AN were 0.003, 0.26, and 0.03, respectively). Thus, in this community-based sample of elderly individuals, those with AF burden of 100% (persistent AF), but not 1–6% (paroxysmal AF) had lower executive and verbal cognitive test scores than those without AF. As hypothesized, these associations remained significant after adjustment for prevalent clinical stroke. However, contrary to our expectation, these associations persisted even after further adjustment for SCIs, refuting our hypothesis that SCIs can explain the relationship between higher AF burden and lower cognitive function.

Our findings are hypothesis-generating because of several limitations. First, this was a small cross-sectional study that only included mostly white participants and evaluated cognitive scores at a single point in time. Second, because of the numerous comparisons, positive findings could be due to chance. Third, since the AF burden distribution was bimodal, we could not evaluate the full spectrum of AF burden.

In conclusion, persistent but not paroxysmal AF is associated with lower cognitive function in community-dwelling elderly individuals. Further prospective research is needed to confirm an association of higher AF burden with greater cognitive decline and higher risk of incident dementia. In addition, further investigation is warranted to elucidate the underlying mechanisms to facilitate discovery of prevention strategies.

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ABBREVIATIONS LIST

AF	Atrial fibrillation
AN	Animal naming
ARIC	Atherosclerosis Risk in Communities
DSB	Digit Span Backwards
MRI	Magnetic resonance imaging
SCI	Subclinical cerebral infarct
TMT	Trail Making Test

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Table

Association of Atrial Fibrillation Burden with *Z*-Scores of Selected Cognitive Tests, Atherosclerosis Risk in Communities Study, Visit 5 (2013–14)

	Model	AF burden, 1–6%, (paroxysmal) (n=14)	p	AF burden=100%, (persistent) (n=12)	p
MMSE	M1	−0.07 (−0.54 to 0.40)	0.77	−0.50 (−1.19 to 0.18)	0.15
	M2	−0.14 (−0.60 to 0.32)	0.54	−0.42 (−1.09 to 0.25)	0.22
DWR	M1	−0.17 (−0.50 to 0.15)	0.30	−0.62 (−1.21 to −0.04)	0.04
	M2	−0.17 (−0.54 to 0.20)	0.37	−0.44 (−1.05 to 0.16)	0.15
ILdsp	M1	−0.44 (−1.05 to 0.18)	0.16	0.02 (−0.88 to 0.92)	0.97
	M2	−0.42 (−1.02 to 0.18)	0.17	−0.12 (−1.17 to 0.93)	0.82
AN	M1	−0.10 (−0.51 to 0.32)	0.65	−0.78 (−1.18 to −0.37)	<0.001
	M2	−0.13 (−0.56 to 0.30)	0.56	−0.81 (−1.25 to −0.38)	<0.001
	M3	−0.13 (−0.55 to 0.29)	0.55	−0.75 (−1.17 to −0.34)	<0.001
	M4	−0.14 (−0.56 to 0.28)	0.52	−0.81 (−1.23 to −0.38)	<0.001
WF	M1	0.02 (−0.58 to 0.62)	0.95	−0.48 (−1.10 to 0.15)	0.14
	M2	−0.01 (−0.58 to 0.56)	0.97	−0.56 (−1.19 to 0.08)	0.08
TMTa	M1	0.37 (−0.14 to 0.88)	0.15	−0.48 (−1.16 to 0.20)	0.16
	M2	0.34 (−0.15 to 0.83)	0.17	−0.42 (−1.15 to 0.32)	0.27
TMTb	M1	0.09 (−0.54 to 0.73)	0.78	−0.64 (−1.42 to 0.15)	0.11
	M2	−0.01 (−0.61 to 0.59)	0.97	−0.76 (−1.42 to −0.09)	0.03
	M3	−0.04 (−0.64 to 0.56)	0.90	−0.70 (−1.32 to −0.07)	0.03
	M4	−0.01 (−0.57 to 0.56)	0.99	−0.59 (−1.19 to 0.00)	0.05
DSS	M1	0.02 (−1.16 to 0.28)	0.94	−0.44 (−1.16 to 0.28)	0.24
	M2	−0.07 (−0.52 to 0.38)	0.77	−0.41 (−1.04 to 0.23)	0.21
DSB	M1	0.55 (0.001 to 1.10)	0.05	−0.75 (−1.46 to −0.05)	0.04
	M2	0.57 (0.03 to 1.10)	0.04	−0.77 (−1.48 to −0.06)	0.03
	M3	0.57 (0.04 to 1.10)	0.04	−0.75 (−1.48 to −0.03)	0.04
	M4	0.57 (−0.04 to 1.10)	0.04	−0.75 (−1.48 to −0.02)	0.04

Analyses were performed using general linear models. No AF (n=299) is the referent group.

M1: Adjusted for age and sex; M2: M1 + educational level, smoking status, body mass index, hypertension, diabetes, coronary heart disease, heart failure, warfarin use, and left ventricular ejection fraction; M3: M2 + prevalent clinical stroke; M4: M3 + presence of subclinical cerebral infarcts

AF=atrial fibrillation; MMSE=mini-mental state examination

Memory: DWR=Delayed Word Recall Test; ILdsp=Incidental Learning, digit-symbol pairs, part B

Verbal fluency: AN=Animal Naming; WF=Word Fluency

Executive function: TMT=Trail Making Test; DSS=Digit Symbol Substitution; DSB=Digit Span Backwards