

## **HHS Public Access**

Author manuscript *J Am Coll Cardiol.* Author manuscript; available in PMC 2017 March 22.

Published in final edited form as:

J Am Coll Cardiol. 2016 March 22; 67(11): 1379–1380. doi:10.1016/j.jacc.2015.11.064.

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

Lin Y. Chen, MD, MS<sup>\*</sup>, Sunil K. Agarwal, MD, PhD<sup>†</sup>, Faye L. Norby, MS, MPH<sup>‡</sup>, Rebecca F. Gottesman, MD, PhD<sup>§</sup>, Laura R. Loehr, MD, PhD<sup>||</sup>, Elsayed Z. Soliman, MD, MSc, MS<sup>¶</sup>, Thomas H. Mosley, PhD<sup>#</sup>, Aaron R. Folsom, MD, MPH<sup>‡</sup>, Josef Coresh, MD, PhD<sup>††</sup>, and Alvaro Alonso, MD, PhD<sup>‡</sup>

\*Cardiovascular Division, Department of Medicine, University of Minnesota Medical School, Minneapolis <sup>†</sup>Department of Medicine, Mount Sinai School of Medicine, New York, New York <sup>‡</sup>Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis <sup>§</sup>Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland <sup>||</sup>Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, North Carolina <sup>¶</sup>Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, North Carolina <sup>#</sup>Department of Medicine, University of Mississippi Medical Center, Jackson <sup>††</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

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

Corresponding author: Lin Y. Chen, MD, 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.

There are no relationships with industry

Chen et al.

brain MRI scans at visit 5/NCS exam wore the Zio<sup>®</sup>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<sup>®</sup>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.

JAm Coll Cardiol. Author manuscript; available in PMC 2017 March 22.

#### Acknowledgments

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Neurocognitive data are collected by U01 HL096812, HL096814, HL096899, HL096902, HL096917. The funder has no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript. The authors thank the staff and participants of the ARIC study for their important contributions.

#### 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

#### References

- 1. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive Impairment Associated With Atrial Fibrillation A Meta-analysis. Ann Intern Med. 2013; 158:338–46. [PubMed: 23460057]
- Chen LY, Lopez FL, Gottesman RF, et al. Atrial fibrillation and cognitive decline-the role of subclinical cerebral infarcts: the atherosclerosis risk in communities study. Stroke. 2014; 45:2568– 74. [PubMed: 25052319]
- Knopman DS, Griswold ME, Lirette ST, et al. Vascular Imaging Abnormalities and Cognition Mediation by Cortical Volume in Nondemented Individuals: Atherosclerosis Risk in Communities-Neurocognitive Study. Stroke. 2015; 46:433–440. [PubMed: 25563642]
- 4. Turakhia MP, Hoang DD, Zimetbaum P, et al. Diagnostic Utility of a Novel Leadless Arrhythmia Monitoring Device. Am J Cardiol. 2013; 112:52–4.

# Table

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

MMSEMI $-007(-0.54 \text{ to} 0.40)$ 077 $-0.50(-1.19 \text{ to} 0.32)$ 013MMSEMI $-0.17(-0.50 \text{ to} 0.32)$ 053 $-0.42(-1.09 \text{ to} 0.22)$ 023MMSEMI $-0.17(-0.50 \text{ to} 0.12)$ 0.30 $-0.22(-1.21 \text{ to} -0.44)$ 013MMSEMI $-0.17(-0.54 \text{ to} 0.20)$ 0.31 $-0.44(-1.051 \text{ to} 0.23)$ 013MMSEMI $-0.17(-0.54 \text{ to} 0.20)$ 0.37 $-0.44(-1.051 \text{ to} 0.32)$ 033MMSEMI $-0.17(-0.54 \text{ to} 0.20)$ 0.47 $-0.44(-1.051 \text{ to} 0.34)$ 043MMSEMI $-0.12(-0.54 \text{ to} 0.20)$ 0.47 $-0.26(-1.171 \text{ to} 0.34)$ 043MVMIMI $-0.12(-0.54 \text{ to} 0.20)$ 053 $-0.26(-1.191 \text{ to} 0.34)$ 040MVSMIP.001(-0.51 \text{ to} 0.250 \text{ to} 0.21 $-0.26(-1.191 \text{ to} 0.34)$ 040MVSMIP.012(-0.54 \text{ to} 0.20)053 $-0.26(-1.191 \text{ to} 0.34)$ 040MVSMIP.012(-0.54 \text{ to} 0.20)053 $-0.26(-1.121 \text{ to} 0.34)$ 041MVSMIP.012(-0.54 \text{ to} 0.20)053 $-0.26(-1.121 \text{ to} 0.34)$ 041MVSMIP.012(-0.54 \text{ to} 0.25)043 $-0.26(-1.210 \text{ to} 0.34)$ 041MVSMIP.012(-0.54 \text{ to} 0.25)043 $-0.26(-1.210 \text{ to} 0.34)$ 043MVSMIP.012(-0.54 \text{ to} 0.25)043 $-0.26(-1.210 \text{ to} 0.34)$ 043MVSMIP.012(-0.54 \text{ to} 0.25)044 $-0.26(-1.210 \text{ to} 0.34)$ 043 <t< th=""><th></th><th>Model</th><th>AF burden, 1–6%, (paroxysmal) (n=14)</th><th>d</th><th>AF burden=100%, (persistent) (n=12)</th><th>d</th></t<>		Model	AF burden, 1–6%, (paroxysmal) (n=14)	d	AF burden=100%, (persistent) (n=12)	d
M2 $-0.14(-0.600.0.32)$ 0.54 $-0.42(-1.090.0.25)$ M1 $-0.17(-0.500.0.15)$ 0.30 $-0.62(-1.210-0.04)$ M2 $-0.17(-0.540.0.20)$ 0.37 $-0.62(-1.210-0.04)$ M2 $-0.17(-0.540.0.20)$ 0.16 $-0.44(-1.05 0.016)$ M1 $-0.44(-1.05 0.013)$ 0.17 $-0.12(-1.1700.033)$ M2 $-0.42(-1.020.0.13)$ 0.17 $-0.12(-1.1700.033)$ M2 $-0.13(-0.550.0.20)$ 0.65 $-0.78(-1.180-0.37)$ M3 $-0.13(-0.550.0.23)$ 0.52 $-0.78(-1.1700.033)$ M4 $-0.13(-0.550.023)$ 0.52 $-0.78(-1.1700.033)$ M3 $-0.14(-0.560.023)$ 0.52 $-0.78(-1.1700.015)$ M4 $-0.11(-0.580.025)$ 0.52 $-0.78(-1.1700.015)$ M3 $-0.14(-0.560.023)$ 0.52 $-0.48(-1.100.015)$ M4 $-0.01(-0.580.025)$ 0.57 $-0.48(-1.100.015)$ M3 $-0.01(-0.580.055)$ 0.57 $-0.48(-1.160.023)$ M4 $-0.01(-0.580.055)$ 0.57 $-0.48(-1.160.015)$ M4 $-0.01(-0.580.055)$ 0.57 $-0.48(-1.160.023)$ M4 $-0.01(-0.580.055)$ 0.77 $-0.76(-1.420.015)$ M4 $-0.01(-0.570.056)$ 0.79 $-0.76(-1.420.015)$ M4 $-0.01(-0.570.056)$ 0.79 $-0.76(-1.420.015)$ M4 $-0.01(-0.570.056)$ 0.91 $-0.76(-1.420.015)$ M4 $-0.01(-0.570.056)$ 0.91 $-0.76(-1.420.016)$ M4 $-0.01(-0.570.058)$ 0.91 $-0.76(-1.420.016)$ M4 $-0.01(-0.570.058)$ 0.91	MMSE	M1	-0.07 (-0.54 to 0.40)	0.77	-0.50 (-1.19 to 0.18)	0.15
MI $-0.17(-0.540 0.015)$ $0.37$ $-0.62(-1.210 - 0.04)$ M2 $-0.17(-0.540 0.20)$ $0.37$ $-0.44(-1.05 to 0.16)$ M1 $-0.141(-105 to 0.18)$ $0.17$ $-0.14(-1.05 to 0.16)$ M1 $-0.141(-1.05 to 0.18)$ $0.17$ $-0.12(-1.17to 0.93)$ M2 $-0.12(-0.51to 0.22)$ $0.56$ $-0.78(-1.18to -0.37)$ M2 $-0.13(-0.56 to 0.20)$ $0.56$ $-0.78(-1.18to -0.37)$ M2 $-0.13(-0.56 to 0.20)$ $0.57$ $-0.78(-1.17to 0.93)$ M3 $-0.13(-0.56 to 0.20)$ $0.57$ $-0.78(-1.17to 0.03)$ M4 $-0.113(-0.56 to 0.20)$ $0.57$ $-0.78(-1.17to 0.03)$ M3 $-0.14(-0.56 to 0.20)$ $0.57$ $-0.78(-1.17to 0.03)$ M4 $-0.113(-0.58 to 0.20)$ $0.57$ $-0.78(-1.17to 0.03)$ M4 $-0.14(-0.56 to 0.20)$ $0.57$ $-0.78(-1.17to 0.03)$ M3 $-0.01(-0.58 to 0.20)$ $0.77$ $-0.48(-1.10to 0.15)$ M4 $-0.01(-0.58 to 0.20)$ $0.77$ $-0.48(-1.10to 0.15)$ M4 $-0.01(-0.58 to 0.50)$ $0.77$ $-0.48(-1.16to 0.23)$ M4 $-0.01(-0.58 to 0.50)$ $0.77$ $-0.48(-1.16to 0.23)$ M4 $-0.01(-0.58 to 0.50)$ $0.77$ $-0.75(-1.48 to 0.00)$ M4 $-0.01(-0.58 to 0.59)$ $0.77$ $-0.76(-1.42 to 0.15)$ M4 $-0.01(-0.58 to 0.50)$ $0.77$ $-0.76(-1.15 to 0.23)$ M4 $-0.01(-0.58 to 0.50)$ $0.78$ $-0.76(-1.16 to 0.26)$ M4 $-0.001(-0.58 to 0.50)$ $0.79$ $-0.76(-1.13 to 0.50)$ M4<		M2	-0.14 (-0.60 to 0.32)	0.54	-0.42 (-1.09 to 0.25)	0.22
M2 $-0.17(-0.54 \text{ tr} 0.20)$ $0.37$ $-0.44(-1.05 \text{ tr} 0.18)$ $0.76$ $-0.44(-1.05 \text{ tr} 0.18)$ M1 $-0.44(-1.05 \text{ tr} 0.18)$ $0.16$ $0.002(-0.88 \text{ tr} 0.92)$ $0.17$ M1 $-0.44(-1.05 \text{ tr} 0.18)$ $0.17$ $-0.12(-1.17 \text{ tr} 0.03)$ $0.17$ M2 $-0.13(-0.55 \text{ tr} 0.23)$ $0.56$ $-0.78(-1.18 \text{ tr} -0.33)$ $0.17$ M2 $-0.13(-0.55 \text{ tr} 0.23)$ $0.57$ $-0.78(-1.18 \text{ tr} -0.34)$ $0.17$ M2 $-0.14(-0.56 \text{ tr} 0.23)$ $0.57$ $-0.78(-1.19 \text{ tr} 0.03)$ $0.31$ M3 $-0.14(-0.58 \text{ tr} 0.25)$ $0.57$ $-0.78(-1.19 \text{ tr} 0.03)$ $0.31$ M3 $-0.14(-0.58 \text{ tr} 0.23)$ $0.57$ $-0.78(-1.19 \text{ tr} 0.03)$ $0.31$ M3 $-0.14(-0.58 \text{ tr} 0.23)$ $0.32$ $-0.38(-1.10 \text{ tr} 0.15)$ $0.31$ M3 $-0.01(-0.58 \text{ tr} 0.23)$ $0.32$ $-0.38(-1.10 \text{ tr} 0.32)$ $0.31$ M3 $-0.01(-0.58 \text{ tr} 0.23)$ $0.32$ $-0.38(-1.19 \text{ tr} 0.03)$ $0.31$ M3 $-0.01(-0.58 \text{ tr} 0.53)$ $0.32$ $-0.38(-1.16 \text{ tr} 0.23)$ M4 $N$ $0.37(-0.14 \text{ tr} 0.83)$ $0.72$ $-0.48(-1.16 \text{ tr} 0.23)$ M3 $N$ $0.32(-0.14 \text{ tr} 0.33)$ $0.72$ $-0.48(-1.16 \text{ tr} 0.23)$ M3 $N$ $0.32(-0.14 \text{ tr} 0.32)$ $0.32$ $-0.24(-1.42 \text{ tr} 0.02)$ M4 $N$ $0.32(-0.14 \text{ tr} 0.23)$ $0.32$ $-0.72(-1.42 \text{ tr} 0.02)$ M3 $N$ $0.03(-0.016 \text{ tr} 0.24 \text{ tr} 0.24)$ $-0.24(-1.42 \text{ tr} 0.20)$ </td <td>DWR</td> <td>M1</td> <td>-0.17 (-0.50 to 0.15)</td> <td>0.30</td> <td>-0.62 (-1.21 to -0.04)</td> <td>0.04</td>	DWR	M1	-0.17 (-0.50 to 0.15)	0.30	-0.62 (-1.21 to -0.04)	0.04
MI $-0.44(-1.05 to 0.18)$ 0.15 $0.02(-0.88 to 0.92)$ M2 $-0.42(-1.02 to 0.18)$ 0.17 $-0.12(-1.17 to 0.93)$ M1 $-0.142(-1.02 to 0.13)$ 0.55 $-0.78(-1.18 to -0.37)$ M1 $-0.13(-0.55 to 0.20)$ 0.55 $-0.81(-1.25 to -0.38)$ M2 $-0.13(-0.55 to 0.20)$ 0.56 $-0.81(-1.25 to -0.38)$ M3 $-0.13(-0.55 to 0.28)$ 0.57 $-0.78(-1.17 to -0.34)$ M4 $-0.14(-0.56 to 0.28)$ 0.57 $-0.78(-1.17 to -0.34)$ M4 $0.012(-0.58 to 0.28)$ 0.57 $-0.48(-1.10 to 0.15)$ M1 $0.027(-0.58 to 0.28)$ 0.57 $-0.48(-1.10 to 0.15)$ M2 $0.02(-0.58 to 0.28)$ 0.97 $-0.48(-1.10 to 0.15)$ M1 $0.027(-0.58 to 0.56)$ 0.97 $-0.48(-1.10 to 0.15)$ M2 $0.02(-0.58 to 0.56)$ 0.97 $-0.48(-1.10 to 0.15)$ M2 $0.02(-0.58 to 0.58)$ 0.97 $-0.48(-1.10 to 0.15)$ M2 $0.02(-0.58 to 0.58)$ 0.97 $-0.48(-1.10 to 0.15)$ M2 $0.02(-0.58 to 0.58)$ 0.97 $-0.42(-1.16 to 0.28)$ M2 $0.02(-0.58 to 0.58)$ 0.97 $-0.56(-1.19 to 0.09)$ M3 $0.09(-0.54 to 0.56)$ 0.97 $-0.56(-1.19 to 0.09)$ M4 $0.001(-0.51 to 0.56)$ 0.97 $-0.76(-1.42 to 0.05)$ M4 $0.001(-0.51 to 0.56)$ 0.97 $-0.56(-1.19 to 0.09)$ M4 $0.001(-0.52 to 0.58)$ 0.97 $-0.76(-1.42 to 0.05)$ M4 $0.022(-0.16 to 0.58)$ 0.97 $-0.76(-1.42 to 0.05)$ M4 $0.02(-0.51 to 0.56)$ <td></td> <td>M2</td> <td>-0.17 (-0.54 to 0.20)</td> <td>0.37</td> <td>-0.44 (-1.05 to 0.16)</td> <td>0.15</td>		M2	-0.17 (-0.54 to 0.20)	0.37	-0.44 (-1.05 to 0.16)	0.15
M2 $-0.42(-1.02  {\rm to} 0.18)$ $0.17$ $-0.12(-1.17  {\rm to} 0.93)$ M1 $-0.10(-0.51  {\rm to} 0.32)$ $0.65$ $-0.78(-1.18  {\rm to} -0.37)$ $-0.78(-1.18  {\rm to} -0.37)$ M2 $-0.13(-0.55  {\rm to} 0.30)$ $0.55$ $-0.81(-1.25  {\rm to} -0.38)$ $-0.13(-0.58  {\rm to} 0.28)$ $-0.13(-0.58  {\rm to} 0.28)$ $-0.13(-0.58  {\rm to} 0.28)$ M3 $-0.13(-0.58  {\rm to} 0.28)$ $0.52$ $-0.81(-1.25  {\rm to} -0.38)$ $-0.13(-0.58  {\rm to} 0.28)$ M4 $-0.14(-0.56  {\rm to} 0.28)$ $0.57$ $-0.81(-1.25  {\rm to} -0.38)$ $-0.31(-0.58  {\rm to} 0.28)$ M1 $0.02(-0.58  {\rm to} 0.26)$ $0.97$ $-0.81(-1.25  {\rm to} 0.38)$ $-0.31(-0.58  {\rm to} 0.28)$ M2 $-0.01(-0.58  {\rm to} 0.56)$ $0.97$ $-0.48(-1.10  {\rm to} 0.15)$ M2 $0.02(-0.54  {\rm to} 0.56)$ $0.97$ $-0.56(-1.19  {\rm to} 0.08)$ M1 $0.09(-0.54  {\rm to} 0.73)$ $0.77$ $-0.48(-1.16  {\rm to} 0.29)$ M2 $0.09(-0.54  {\rm to} 0.73)$ $0.77$ $-0.48(-1.16  {\rm to} 0.29)$ M3 $0.09(-0.54  {\rm to} 0.73)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M4 $0.09(-0.54  {\rm to} 0.73)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M3 $0.09(-0.54  {\rm to} 0.73)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M4 $0.09(-0.54  {\rm to} 0.56)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M4 $0.09(-0.54  {\rm to} 0.56)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M4 $0.09(-0.54  {\rm to} 0.56)$ $0.97$ $-0.76(-1.42  {\rm to} 0.93)$ M4 $0.09(-0.52  {\rm to}$	ILdsp	M1	-0.44 (-1.05 to 0.18)	0.16	0.02 (-0.88 to 0.92)	0.97
MI -0.10(-0.51 tb 0.32) 0.65 -0.78(-1.18 tb -0.37) N   M2 -0.13(-0.56 tb 0.30) 0.56 -0.81(-1.25 tb -0.38) N   M3 -0.13(-0.56 tb 0.28) 0.55 -0.75(-1.17 tb -0.34) N   M4 0.014(-0.56 tb 0.28) 0.52 -0.75(-1.17 tb -0.34) N   M1 0.012(-0.58 tb 0.62) 0.97 -0.81(-1.25 tb -0.38) N   M1 0.012(-0.58 tb 0.62) 0.97 -0.81(-1.25 tb -0.38) N   M2 0.012(-0.58 tb 0.62) 0.97 -0.48(-1.10 tb 0.15) N   M1 0.02(-0.58 tb 0.62) 0.97 -0.48(-1.16 tb 0.28) N   M1 0.037(-0.14 tb 0.88) 0.17 -0.48(-1.16 tb 0.28) N   M2 0.37(-0.14 tb 0.88) 0.17 -0.42(-1.15 tb 0.32) N   M1 0.03(-0.54 tb 0.56) 0.97 -0.76(-1.42 tb 0.05) N   M3 0.010(-0.61 tb 0.59) 0.97 -0.76(-1.42 tb 0.05) N   M3 0.001(-0.51 tb 0.56) 0.97 -0.76(-1.42 tb 0.05) N		M2	-0.42 (-1.02 to 0.18)	0.17	-0.12 (-1.17 to 0.93)	0.82
M2 -0.13 (-0.56 to 0.30) 0.56 -0.081 (-1.25 to -0.38)   M3 -0.13 (-0.56 to 0.28) 0.55 -0.75 (-1.17 to -0.34)   M4 -0.14 (-0.56 to 0.28) 0.55 -0.75 (-1.17 to -0.34)   M4 -0.14 (-0.56 to 0.28) 0.55 -0.81 (-1.23 to -0.38) -   M1 0.002 (-0.58 to 0.62) 0.97 -0.48 (-1.10 to 0.15) -   M2 -0.01 (-0.58 to 0.56) 0.97 -0.48 (-1.16 to 0.20) -   M2 0.37 (-0.14 to 0.88) 0.17 -0.48 (-1.16 to 0.20) -   M1 0.37 (-0.14 to 0.88) 0.17 -0.48 (-1.16 to 0.20) -   M2 0.34 (-0.15 to 0.83) 0.17 -0.48 (-1.16 to 0.20) -   M1 0.09 (-0.54 to 0.73) 0.78 -0.64 (-1.42 to 0.15) -   M2 0.09 (-0.54 to 0.73) 0.77 -0.48 (-1.16 to 0.20) -   M2 0.09 (-0.54 to 0.73) 0.78 -0.76 (-1.42 to 0.15) -   M2 0.01 (-0.51 to 0.56) 0.79 -0.76 (-1.42 to 0.15) -   M2 0.01 (-0	AN	M1	-0.10 (-0.51 to 0.32)	0.65	-0.78 (-1.18  to  -0.37)	<0.001
M3 $-0.13(-0.55 to 0.29)$ 0.55 $-0.75(-1.17 to -0.34)$ M4 $-0.14(-0.56 to 0.28)$ $0.52$ $-0.81(-1.23 to -0.38)$ M1 $0.02(-0.58 to 0.62)$ $0.95$ $-0.48(-1.10 to 0.15)$ M2 $-0.01(-0.58 to 0.56)$ $0.97$ $-0.56(-1.19 to 0.08)$ M2 $-0.01(-0.58 to 0.56)$ $0.97$ $-0.48(-1.16 to 0.20)$ M1 $0.37(-0.14 to 0.88)$ $0.17$ $-0.64(-1.42 to 0.8)$ M1 $0.37(-0.14 to 0.88)$ $0.17$ $-0.48(-1.16 to 0.20)$ M1 $0.37(-0.14 to 0.89)$ $0.17$ $-0.48(-1.16 to 0.20)$ M2 $0.37(-0.14 to 0.59)$ $0.78$ $-0.48(-1.16 to 0.20)$ M1 $0.09(-0.54 to 0.73)$ $0.79$ $-0.42(-1.42 to 0.09)$ M2 $0.09(-0.54 to 0.73)$ $0.79$ $-0.70(-1.42 to 0.09)$ M2 $0.09(-0.54 to 0.59)$ $0.97$ $-0.76(-1.42 to -0.09)$ M3 $0.09(-0.54 to 0.59)$ $0.97$ $-0.76(-1.42 to -0.09)$ M4 $0.09(-0.54 to 0.50)$ $0.97$ $-0.77(-1.42 to 0.05)$ M4 $0.02(-1.16 to 0.58)$ $0.97$ $-0.77(-1.42 to -0.09)$ M1 $0.02(-1.16 to 0.28)$ $0.94$ $-0.77(-1.42 to -0.09)$ M1 $0.02(-1.16 to 0.28)$ $0.94$ $-0.77(-1.42 to -0.05)$ M1 $0.02(-1.16 to 0.28)$ $0.94$ $-0.77(-1.48 to -0.05)$ M2 $0.02(-1.16 to 0.28)$ $0.94$ $-0.77(-1.48 to -0.05)$ M1 $0.57(0.03 to 1.10)$ $0.79$ $-0.75(-1.48 to -0.05)$ M3 $0.57(0.04 to 1.10)$ $0.04$ $-0.75(-1.48 to -0.05)$ M3<		M2	-0.13 (-0.56 to 0.30)	0.56	-0.81 (-1.25 to -0.38)	<0.001
M4-0.14(-0.56 to 0.28)0.52-0.81(-1.23 to -0.38)M10.02(-0.58 to 0.62)0.95-0.48(-1.10 to 0.15)M20.01(-0.58 to 0.56)0.97-0.56(-1.19 to 0.08)M10.37(-0.14 to 0.83)0.15-0.48(-1.16 to 0.20)M20.37(-0.14 to 0.83)0.17-0.42(-1.15 to 0.20)M20.34(-0.15 to 0.83)0.17-0.42(-1.15 to 0.20)M20.34(-0.15 to 0.83)0.17-0.42(-1.42 to 0.15)M20.09(-0.54 to 0.73)0.78-0.64(-1.42 to 0.15)M30.01(-0.61 to 0.59)0.97-0.64(-1.42 to 0.15)M30.001(-0.61 to 0.59)0.90-0.76(-1.32 to -0.07)M40.001(-0.61 to 0.50)0.91-0.76(-1.42 to 0.05)M40.010(-0.57 to 0.56)0.90-0.76(-1.42 to 0.05)M40.010(-0.51 to 0.50)0.91-0.76(-1.42 to 0.05)M40.010(-0.51 to 0.50)0.92-0.76(-1.42 to 0.05)M40.010(-0.51 to 0.50)0.91-0.76(-1.42 to 0.05)M10.02(-1.16 to 0.58)0.91-0.76(-1.42 to 0.05)M20.02(-1.16 to 0.58)0.91-0.76(-1.42 to 0.05)M40.02(-1.16 to 0.58)0.91-0.76(-1.42 to 0.05)M40.02(-1.16 to 0.58)0.91-0.76(-1.42 to 0.05)M40.010.92-0.76(-0.40 to 0.23)M20.02(-1.16 to 0.58)0.91-0.76(-1.42 to 0.05)M40.057(0.03 to 1.10)0.04-0.77(-1.48 to -0.05)M40.57(0.04 to 1.10)0.04-0.7		M3	-0.13 (-0.55 to 0.29)	0.55	-0.75 (-1.17 to -0.34)	<0.001
MI0.02 (-0.58 to 0.62)0.95-0.48 (-1.10 to 0.15)M2-0.01 (-0.58 to 0.56)0.97-0.56 (-1.19 to 0.08)M10.37 (-0.14 to 0.88)0.15-0.48 (-1.16 to 0.20)M20.37 (-0.14 to 0.83)0.17-0.42 (-1.15 to 0.32)M20.34 (-0.15 to 0.83)0.17-0.42 (-1.15 to 0.32)M20.34 (-0.15 to 0.73)0.78-0.42 (-1.15 to 0.32)M10.09 (-0.54 to 0.73)0.79-0.64 (-1.42 to 0.15)M20.09 (-0.54 to 0.56)0.97-0.76 (-1.42 to 0.15)M3-0.01 (-0.61 to 0.59)0.97-0.76 (-1.42 to 0.09)M30.09 (-0.54 to 0.73)0.97-0.76 (-1.42 to 0.15)M3-0.01 (-0.51 to 0.59)0.97-0.76 (-1.42 to 0.09)M40.02 (-1.16 to 0.59)0.97-0.76 (-1.42 to 0.05)M10.02 (-1.16 to 0.28)0.94-0.76 (-1.42 to 0.05)M30.02 (-1.16 to 0.28)0.94-0.74 (-1.16 to 0.28)M40.02 (-1.16 to 0.28)0.94-0.74 (-1.16 to 0.28)M10.02 (-1.16 to 0.28)0.94-0.75 (-1.46 to -0.05)M30.57 (0.01 to 1.10)0.05-0.75 (-1.46 to -0.05)M40.57 (0.04 to 1.10)0.04-0.75 (-1.48 to -0.06)M30.57 (0.04 to 1.10)0.04-0.75 (-1.48 to -0.05)M40.57 (0.04 to 1.10)0.04-0.75 (-1.48 to -0.05)		M4	-0.14 (-0.56 to 0.28)	0.52	-0.81 (-1.23 to -0.38)	<0.001
M2 -0.01 (-0.58 to 0.56) 0.97 -0.56 (-1.19 to 0.08)   M1 0.37 (-0.14 to 0.88) 0.15 -0.48 (-1.16 to 0.20)   M2 0.34 (-0.15 to 0.83) 0.17 -0.48 (-1.16 to 0.20)   M2 0.34 (-0.15 to 0.83) 0.17 -0.42 (-1.15 to 0.32)   M1 0.04 (-0.54 to 0.73) 0.78 -0.42 (-1.15 to 0.32)   M1 0.09 (-0.54 to 0.73) 0.78 -0.42 (-1.15 to 0.32)   M2 0.09 (-0.54 to 0.73) 0.79 -0.42 (-1.42 to 0.15)   M2 0.00 (-0.51 to 0.59) 0.97 -0.76 (-1.42 to 0.09)   M3 0.00 (-0.51 to 0.56) 0.97 -0.76 (-1.42 to 0.09)   M4 0.01 (-0.57 to 0.56) 0.99 -0.76 (-1.42 to 0.09)   M4 0.001 (-0.57 to 0.58) 0.97 -0.76 (-1.42 to 0.09)   M2 0.02 (-1.16 to 0.28) 0.97 -0.44 (-1.16 to 0.28)   M2 0.02 (-1.16 to 0.28) 0.97 -0.75 (-1.48 to -0.05)   M1 0.05 (0.001 to 1.10) 0.07 -0.77 (-1.48 to -0.05)   M2 0.57 (0.04 to 1.10) 0.04 -0.77 (-	WF	M1	0.02 (-0.58 to 0.62)	0.95	-0.48 (-1.10 to 0.15)	0.14
MI 0.37 (-0.14 to 0.88) 0.15 -0.48 (-1.16 to 0.20)   MZ 0.34 (-0.15 to 0.83) 0.17 -0.42 (-1.15 to 0.32)   MI 0.09 (-0.54 to 0.73) 0.17 -0.42 (-1.15 to 0.32)   MZ 0.09 (-0.54 to 0.73) 0.78 -0.64 (-1.42 to 0.15)   MZ -0.01 (-0.61 to 0.59) 0.97 -0.76 (-1.42 to 0.16)   MZ -0.01 (-0.51 to 0.55) 0.90 -0.76 (-1.42 to 0.16)   MZ -0.01 (-0.57 to 0.56) 0.90 -0.76 (-1.42 to 0.16)   MZ -0.01 (-0.57 to 0.56) 0.90 -0.76 (-1.42 to 0.16)   MZ -0.01 (-0.57 to 0.56) 0.90 -0.76 (-1.42 to 0.16)   MZ -0.01 (-0.57 to 0.56) 0.90 -0.76 (-1.42 to 0.07)   MZ 0.02 (-1.16 to 0.28) 0.91 -0.74 (-1.16 to 0.28)   MZ 0.02 (-1.16 to 0.28) 0.77 -0.44 (-1.16 to 0.28)   MZ 0.02 (-0.110 to 1.10) 0.07 -0.75 (-1.46 to -0.05)   MZ 0.55 (0.001 to 1.10) 0.04 -0.77 (-1.48 to -0.05)   MZ 0.57 (0.04 to 1.10) 0.04 -0.		M2	-0.01 (-0.58 to 0.56)	70.07	-0.56 (-1.19 to 0.08)	0.08
M2 0.34 (-0.15 to 0.83) 0.17 -0.42 (-1.15 to 0.32)   M1 0.09 (-0.54 to 0.73) 0.78 -0.64 (-1.42 to 0.15)   M2 -0.01 (-0.61 to 0.59) 0.79 -0.54 (-1.42 to 0.15)   M3 -0.01 (-0.61 to 0.59) 0.97 -0.76 (-1.42 to 0.09)   M3 -0.04 (-0.64 to 0.56) 0.90 -0.70 (-1.32 to -0.07)   M4 0.02 (-1.16 to 0.28) 0.90 -0.70 (-1.32 to -0.07)   M4 0.02 (-1.16 to 0.28) 0.91 -0.70 (-1.32 to -0.07)   M1 0.02 (-1.16 to 0.28) 0.92 -0.74 (-1.16 to 0.28)   M2 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28)   M1 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28)   M2 0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.04 to 0.23)   M2 0.057 (0.001 to 1.10) 0.06 -0.75 (-1.48 to -0.06)   M2 0.57 (0.04 to 1.10) 0.04 -0.77 (-1.48 to -0.05)   M3 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05)   M4 0.057 (-0.04 to 1.10) 0.04 -	TMTa	M1	0.37 (-0.14 to 0.88)	0.15	-0.48 (-1.16 to 0.20)	0.16
MI 0.09 (-0.54 to 0.73) 0.78 -0.64 (-1.42 to 0.15)    MZ -0.01 (-0.61 to 0.59) 0.97 -0.76 (-1.42 to -0.09)    M3 -0.04 (-0.64 to 0.56) 0.90 -0.76 (-1.42 to -0.09)    M4 -0.01 (-0.57 to 0.56) 0.90 -0.70 (-1.32 to -0.07)    M4 -0.01 (-0.57 to 0.56) 0.99 -0.70 (-1.32 to -0.07)    M1 0.02 (-1.16 to 0.28) 0.94 -0.59 (-1.19 to 0.00)    M1 0.02 (-1.16 to 0.28) 0.94 -0.54 (-1.16 to 0.28)    M2 0.02 (-1.16 to 0.28) 0.77 -0.44 (-1.16 to 0.28)    M1 0.02 (-1.16 to 0.28) 0.77 -0.74 (-1.04 to 0.23)    M2 0.057 (0.01 to 1.10) 0.07 -0.75 (-1.48 to -0.05)    M2 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05)    M3 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.02)		M2	0.34 (-0.15 to 0.83)	0.17	-0.42 (-1.15 to 0.32)	0.27
M2 -0.01 (-0.61 to 0.59) 0.97 -0.76 (-1.42 to -0.09)    M3 -0.04 (-0.64 to 0.56) 0.90 -0.70 (-1.32 to -0.07)    M4 -0.01 (-0.57 to 0.56) 0.99 -0.70 (-1.32 to -0.07)    M1 0.02 (-1.16 to 0.28) 0.91 -0.65 (-1.19 to 0.00)    M1 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28)    M2 0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.28)    M2 0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.28)    M1 0.05 (0.001 to 1.10) 0.78 -0.77 (-1.48 to -0.05)    M2 0.57 (0.03 to 1.10) 0.05 -0.77 (-1.48 to -0.05)    M3 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05)    M4 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.02)	dTMTb	M1	0.09 (-0.54 to 0.73)	0.78	-0.64 (-1.42 to 0.15)	0.11
M3 -0.04 (-0.54 to 0.56) 0.90 -0.70 (-1.32 to -0.07) 1   M4 -0.01 (-0.57 to 0.56) 0.99 -0.59 (-1.19 to 0.00) 1   M1 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28) 1   M2 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28) 1   M2 0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.28) 1   M1 0.05 (0.001 to 1.10) 0.77 -0.44 (-1.46 to -0.05) 1   M2 0.57 (0.03 to 1.10) 0.05 -0.77 (-1.48 to -0.05) 1   M3 0.57 (0.04 to 1.10) 0.04 -0.77 (-1.48 to -0.05) 1   M4 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05) 1		M2	-0.01 (-0.61 to 0.59)	0.97	-0.76 (-1.42 to -0.09)	0.03
M4 -0.01 (-0.57 to 0.56) 0.99 -0.59 (-1.19 to 0.00)   M1 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28) 7   M2 -0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.28) 7   M2 -0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.23) 7   M2 -0.07 (-0.52 to 0.38) 0.77 -0.44 (-1.16 to 0.23) 7   M1 0.55 (0.001 to 1.10) 0.05 -0.77 (-1.46 to -0.05) 7   M2 0.57 (0.03 to 1.10) 0.04 -0.77 (-1.48 to -0.05) 7   M3 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05) 7   M4 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05) 7		M3	-0.04 (-0.64 to 0.56)	0.90	-0.70 (-1.32 to -0.07)	0.03
M1 0.02 (-1.16 to 0.28) 0.94 -0.44 (-1.16 to 0.28)   M2 -0.07 (-0.52 to 0.38) 0.77 -0.41 (-1.04 to 0.23)   M1 0.55 (0.001 to 1.10) 0.05 -0.75 (-1.46 to -0.05)   M2 0.57 (0.03 to 1.10) 0.05 -0.77 (-1.48 to -0.05)    M3 0.57 (0.04 to 1.10) 0.04 -0.77 (-1.48 to -0.05)    M4 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05)		M4	-0.01 (-0.57 to 0.56)	0.99	-0.59 (-1.19 to 0.00)	0.05
M2 -0.07 (-0.52 to 0.38) 0.77 -0.41 (-1.04 to 0.23)   M1 0.55 (0.001 to 1.10) 0.05 -0.75 (-1.46 to -0.05)    M2 0.57 (0.03 to 1.10) 0.05 -0.77 (-1.48 to -0.06)    M3 0.57 (0.04 to 1.10) 0.04 -0.77 (-1.48 to -0.05)    M4 0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05)	DSS	M1	0.02 (-1.16 to 0.28)	0.94	-0.44 (-1.16 to 0.28)	0.24
M1 0.55 (0.001 to 1.10) 0.05 -0.75 (-1.46 to -0.05) 0   M2 0.57 (0.03 to 1.10) 0.04 -0.77 (-1.48 to -0.06) 1   M3 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.05) 1   M4 0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.03) 1		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
0.57 (0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.03)   0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.02)		M2	0.57 (0.03 to 1.10)	0.04	-0.77 (-1.48 to -0.06)	0.03
0.57 (-0.04 to 1.10) 0.04 -0.75 (-1.48 to -0.02)		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

J Am Coll Cardiol. Author manuscript; available in PMC 2017 March 22.

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 creebral infarcts

Author Manuscript

# Author Manuscript

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