ORIGINAL RESEARCH

Correlates of Dementia and Mild Cognitive Impairment in Patients With Atrial Fibrillation: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

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***Background*—**Atrial fibrillation (AF) has been associated with faster cognitive decline and increased dementia risk. Factors associated with dementia in patients with AF have been seldom studied.

***Methods and Results*—**We studied 6432 individuals from the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). In 2011 to 2013, participants underwent a physical exam, echocardiography, detailed cognitive assessments, and a subset, brain magnetic resonance imaging. Dementia and mild cognitive impairment (MCI), as well as etiology of MCI/dementia, Alzheimer's disease–related or vascular, were adjudicated by an expert panel. AF was defined by study ECGs and past hospitalizations. We used logistic regression to estimate odds ratios and 95% CI of MCI/dementia by AF status and to assess cross-sectional correlates of MCI/dementia in patients with AF. Among 6432 participants, 611 (9.5%) had prevalent AF. AF was associated with increased odds of dementia and MCI (odds ratio, 95% CI, 2.25, 1.64–3.10, and 1.28, 1.04–1.56, respectively). Prevalence of Alzheimer's disease–related MCI/dementia and vascular MCI/dementia were higher in participants with AF than without AF (odds ratio, 95% CI, 1.29, 1.04–1.61, and 1.50, 0.99–2.25, respectively). In multivariable analyses, older age, lower body mass index, diabetes mellitus, stroke, and *APOE* genotype were associated with dementia prevalence in participants with AF. In models evaluating MCI/dementia subtypes, diabetes mellitus was associated with Alzheimer's disease–related MCI/dementia, whereas male sex and stroke were risk factors for vascular MCI/dementia.

***Conclusions*—**In a large, community-based study, AF was associated with higher prevalence of MCI and dementia. Controlling cardiometabolic risk factors is a potential target for prevention of adverse cognitive outcomes in AF patients. **(*J Am Heart Assoc.* 2017;6:e006014. DOI: 10.1161/JAHA.117.006014.)**

Key Words: atrial fibrillation • cognitive impairment • dementia • risk factor

Patients with atrial fibrillation (AF), a common cardiac arrhythmia, experience increased mortality and higher rates of stroke, heart failure, and coronary artery disease.[1] In addition, AF possibly leads to faster cognitive decline and development of dementia, even among individuals without a history of stroke.[2,3] Multiple mechanisms could contribute to cognitive impairment in patients with AF, including occurrence of cerebrovascular disease (both overt clinical strokes and silent cerebral infarcts), brain hypoperfusion caused by reduced cardiac output, a proinflammatory state in the context of AF, and microhemorrhages secondary to oral anticoagulation.[4] Whether these factors cause cognitive decline in persons with AF, and to what extent they do, remains an open question.

Understanding the correlates and risk factors of cognitive decline and dementia in patients with AF can provide insights into the pathophysiology of neurodegeneration in the context of

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Accompanying Tables S1 and S2 are available at http://jaha.ahajournals.org/content/6/7/e006014/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In a large, community-based elderly cohort, prevalence of mild cognitive impairment and dementia in individuals with atrial fibrillation (AF) was approximately 40%, higher than in individuals without AF.
- Prevalence of both Alzheimer's disease–type and vascular cognitive impairment were increased in AF patients compared with those without AF.
- Diabetes mellitus was a strong predictor for prevalence of all-cause dementia and, specifically, Alzheimer's disease–type mild cognitive impairment and dementia, whereas stroke history was associated with increased prevalence of vascular mild cognitive impairment and dementia.

What Are the Clinical Implications?

- The high prevalence of mild cognitive impairment and dementia among AF patients may hinder their involvement in the management of their disease.
- Clinicians, caregivers, and patients need to recognize this problem and develop approaches that will lead to optimal outcomes.
- Similarly, identifying effective strategies that slow cognitive decline and prevent dementia in patients with AF is of paramount importance to improve outcomes in these patients.

the arrhythmia. This knowledge may also help identify patients at high risk of cognitive complications and, eventually, may lead to the development of therapeutic approaches specifically tailored to prevent cognitive impairment and dementia in this patient population. The few studies that have assessed determinants of cognitive impairment or dementia in patients with AF have found older age and increased CHA_2DS_2-VASc score (a clinical prediction rule for estimating risk of stroke in AF patients)[5] as consistent predictors of negative cognitive outcomes. However, these studies had limited sample size, suboptimal cognitive phenotyping, or lacked patient diversity.[6–9]

To address existing gaps in the literature and explore potential mechanisms of cognitive impairment in AF, we explored a wide range of potential correlates of prevalent mild cognitive impairment (MCI) and dementia among persons with AF participating in the community-based ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive study). Participants in the ARIC-NCS underwent a detailed cognitive assessment and had extensive information on cardiovascular risk factors.

Methods

Study Population

The ARIC (Atherosclerosis Risk in Communities) study is a community-based prospective cohort with the overall aim of understanding the development of cardiovascular diseases and their risk factors in the general population. In 1987 to 1989, 15 792 men and women aged 45 to 64 years were recruited from 4 communities in the United States: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis suburbs, Minnesota; and Washington County, Maryland.[10] After a baseline exam (visit 1), participants underwent 4 additional exams in 1990 to 1992, 1993 to 1995, 1996 to 1998, and 2011 to 2013 (visits 2–5).

The ARIC-NCS is an ancillary study to the main ARIC study designed to evaluate the role of midlife cardiovascular risk factors on late-life cognitive decline and dementia. As part of the ARIC-NCS, all ARIC participants attending the 2011 to 2013 exam (visit 5) were invited to undergo an extensive cognitive evaluation and, in a selected subset, a more detailed assessment including a neurological exam and brain MRI.[11] ARIC participants were included in this analysis if they participated in visit 5 and provided consent to the use of their genetic data. Because of small numbers, we excluded participants reporting race other than white or black, and nonwhites in the Minneapolis and Washington County field centers.

The ARIC study and ARIC-NCS have been approved by institutional review boards at all participating institutions. Participants provided written informed consent before the exam.

Prevalent AF

Presence of AF at visit 5 was defined as evidence of AF in a standard 12-lead ECG performed during the study exam, or a past history of AF defined as evidence of AF in any previous study ECG or presence of International Classification of Diseases, Ninth Revision Clinical Modification codes 427.31 or 427.32 in any hospitalization occurring during follow-up before visit 5.[12]

Definition of MCI and Dementia

The methodology used to define MCI or dementia among ARIC-NCS participants has been described in detail elsewhere.[11] Briefly, information obtained from a comprehensive neurocognitive battery followed by a neurological exam, detailed neurological history, informant interviews, and brain MRI in selected participants was reviewed by a panel of neurologists and neuropsychologists. This panel classified participants as normal, MCI, or dementia following the criteria proposed by the National Institute of Aging–Alzheimer's Association workgroups.[13,14]

Definition of Alzheimer's Disease–Related and Vascular MCI/Dementia

Based on information collected during the study visit, the panel of reviewers assigned an etiological diagnosis to

participants seen at visit 5 and diagnosed with MCI or dementia. Reviewers could diagnose more than 1 etiology, but were required to assign a primary diagnosis. The diagnosis of Alzheimer's disease (AD)-related MCI/dementia followed the National Institute of Aging–Alzheimer's Association workgroups criteria and was based on the presence of a nonabrupt cognitive syndrome including memory impairment in the absence of features of other specific causes of cognitive impairment.[13,14] The diagnosis of vascular MCI/dementia was based on the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, which use information on a past history of stroke, its temporal relationship with the onset of cognitive impairment, the presence of vascular disease on imaging, and neurological signs of stroke in a physical examination.[15] Criteria in the ARIC study for other etiologies have been described elsewhere.[11]

Covariates

As part of ARIC visit 5, study participants completed questionnaires, underwent a clinical exam, and provided blood and urine samples. Participants reported date of birth, sex, race, education at baseline, and alcohol intake and smoking status at visit 5. Participants were asked to bring all medications and supplements they used over the previous 2 weeks. Weight and height were measured with the participant wearing light clothes. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Blood pressure was measured 3 times after a 5-minute rest. Systolic and diastolic blood pressure were calculated as the average of the second and third measurements. Hypertension was defined as a systolic blood pressure $\geq$140, diastolic blood pressure $\geq$90, or use of antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose $\geq$126 mg/dL, a nonfasting glucose $\geq$200 mg/dL, using medication for diabetes mellitus, or self-reported physician diagnosis of diabetes mellitus. Heart failure, coronary heart disease, and stroke were defined based on presence of adjudicated events according to previously published criteria.[16–18] The CHA_2DS_2-VASc and HAS-BLED scores for risk stratification in patients with AF were calculated based on information available from the study visit.[5,19] Heart rate was calculated from a standard 10-second 12-lead ECG. Circulating N-terminal prohormone of B-type natriuretic peptide, high-sensitivity troponin T, high-sensitivity C-reactive protein, cystatin C, and creatinine were measured in blood samples collected at the visit. Estimated glomerular filtration rate was calculated based on circulating creatinine and cystatin C levels using the Chronic Kidney Disease Epidemiology Collaboration formula.[20] *APOE* genotyping was performed as previously described using the TaqMan assay (Applied Biosystems, Foster City, CA).[21] All ARIC participants that attended the study clinic at visit 5 were invited to undergo a transthoracic echocardiographic study.[22] Left ventricular (LV) ejection fraction, LV mass index, and left atrial volume index were calculated as previously described.[22] Finally, a subset of ARIC visit 5 participants were selected to undergo brain MRI. All individuals without MRI contraindications and who had evidence of cognitive impairment or cognitive decline or had a brain MRI done in a previous exam were invited to undergo brain MRI, as well as a random sample of the remaining participants.[23] White matter hyperintensities, brain infarcts, and microhemorrhages were defined as previously described.[23]

Statistical Analysis

All analyses were conducted using SAS software (volume 9.4; SAS Institute Inc, Cary, NC). We calculated odds ratios (OR) and 95% CI of MCI or dementia by AF status using multinomial logistic regression, adjusting for age, sex, race, education, smoking, BMI, diabetes mellitus, hypertension, alcohol consumption, *APOE* genotype, and prevalent cardiovascular disease (heart failure, stroke, or coronary heart disease). In subsequent analyses restricted to individuals with prevalent AF, we ran age-, sex-, and race-adjusted multinomial logistic models exploring associations of each covariate of interest with prevalence of dementia or MCI. Covariates were selected based on their availability and potential relationship with cognitive impairment, AF, and AF-related outcomes. All covariates showing statistically significant associations ($P<0.05$) were included simultaneously in a multivariable model. The covariates studied, all assessed at visit 5 except education, which was assessed at visit 1, were: education, alcohol consumption, smoking, BMI, diabetes mellitus, hypertension, heart failure, coronary heart disease, stroke, CHA_2DS_2-VASc score, HAS-BLED score, heart rate, estimated glomerular rate, N-terminal prohormone of B-type natriuretic peptide, high-sensitivity C-reactive protein, high-sensitivity troponin T, *APOE* genotype, LV ejection fraction, LV mass index, and left atrial volume index. The same set of analyses was repeated using primary AD-related MCI/dementia and primary vascular MCI/dementia as the outcome variables. Finally, we performed similar analyses in participants who underwent brain MRI and explored the association of white matter hyperintensities (modeled as $\log_2$), presence of infarcts (yes/no), and presence of microhemorrhages (yes/no) with MCI and dementia in logistic models adjusted for age, sex, and race. We also assessed the association of CHA_2DS_2-VASc score, as a continuous variable, with the volume of white matter hyperintensities (log-transformed) and the prevalence of infarcts or microhemorrhages.

Missing values in the covariates and the primary outcome were imputed with multiple imputation using chained equations creating 20 imputed data sets using SAS PROC MI.[24] Imputation models included all variables listed in Table 1. Analyses were conducted separately in each data set, and results were combined using SAS PROC MIANALYZE.

Table 1. Selected Participant Characteristics by AF Status, ARIC 2011 to 2013

	No AF	AF
N	5821	611
Age, y	76 (5)	79 (5)
Women, %	60	46
Blacks, %	24	12
>High school, %	44	39
Alcohol intake, g/w	28 (65)	32 (68)
Current smoker, %	6	6
BMI, kg/m^2	29 (6)	29 (6)
Hypertension, %	74	78
Diabetes mellitus, %	33	42
Heart failure, %	4	26
Coronary heart disease, %	13	31
Stroke, %	4	10
Anticoagulant use, %	3	54
CHA_2DS_2-VASc	3.5 (1.2)	4.2 (1.5)
HAS-BLED	2.7 (0.7)	2.8 (0.8)
Heart rate, bpm	63 (10)	66 (13)
MMSE, score	27.3 (3.1)	26.6 (3.7)
eGFR, mL/min per 1.73 m^2	66 (18)	58 (19)
NT-proBNP*	126 (65, 242)	572 (217, 1315)
hs-CRP*	2.0 (0.9, 4.2)	2.7 (1.4, 5.5)
Troponin T*	1.0 (0.7, 1.6)	1.5 (1.1, 2.6)
APOE ε4 allele, %	29	27
Ejection fraction, %	65 (6)	61 (10)
LVMI, g per m^2	79 (20)	92 (28)
LAVI, mL per m^2	25 (8)	36 (16)
WMH volume, cm^3	17 (17)	21 (20)
Brain infarct, %	25	31
Microhemorrhage, %	24	29

Values correspond to mean (SD) or percent, unless otherwise stated. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LAVI, left atrial volume index; LVMI, left ventricular mass index; MMSE, Mini–Mental State Examination; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; WMH, white matter hyperintensities.
*Median (25th percentile, 75th percentile).

Results

Of 6538 ARIC visit 5 participants, 6432 met the inclusion criteria. Of these, 611 (9.5%) had a diagnosis of AF. As expected, persons with AF were older, more likely to be men and white, and with an overall higher burden of cardiovascular risk factors than those without AF (Table 1). Prevalence of MCI and dementia was 20.6% and 4.8%, respectively, in those without AF and 27.6% and 11.2% in those with AF. In addition, prevalence of AD-related MCI/dementia and vascular MCI/dementia was 16.4% and 3.1% in those without AF and 21.8% and 5.2% in those with AF. After adjustment for sociodemographic and cardiovascular risk factors, the ORs (95% CI) of MCI and dementia associated with AF were 1.28 (1.04, 1.56) and 2.25 (1.64, 3.10), respectively (Table 2). Similarly, odds of both AD-related MCI/dementia (OR [95% CI], 1.29 [1.04, 1.61]) and vascular MCI/dementia (OR [95% CI], 1.50 [0.99, 2.25]) were higher in participants with AF than those without AF, after adjustment for sociodemographic and cardiovascular risk factors (Table 2, model 2). Additional adjustment for prevalent stroke or restricting the analysis to those without prevalent stroke removed the association of AF with vascular

Table 2. Association of Prevalent AF With Prevalence of MCI and Dementia and Prevalence of AD-Related and Vascular MCI/Dementia, ARIC Study, 2011 to 2013

	Odds ratios (95% CIs)		
	Normal	MCI	Dementia
AF	374 (61%)	169 (28%)	68 (11%)
No AF	4345 (75%)	1197 (20%)	279 (5%)
Model 1	1 (ref)	1.32 (1.08, 1.61)	2.17 (1.60, 2.95)
Model 2	1 (ref)	1.28 (1.04, 1.56)	2.25 (1.64, 3.10)
Model 3	1 (ref)	1.20 (0.97, 1.48)	2.00 (1.43, 2.79)
Model 4	1 (ref)	1.24 (1.00, 1.54)	2.01 (1.40, 2.89)
	Normal	AD-related MCI/dementia	Vascular MCI/dementia
AF	370 (69%)	133 (25%)	32 (6%)
No AF	4317 (79%)	957 (18%)	182 (3%)
Model 1	1 (ref)	1.32 (1.06, 1.64)	1.63 (1.09, 2.45)
Model 2	1 (ref)	1.29 (1.04, 1.61)	1.50 (0.99, 2.25)
Model 3	1 (ref)	1.29 (1.03, 1.62)	0.90 (0.57, 1.43)
Model 4	1 (ref)	1.28 (1.01, 1.62)	0.87 (0.49, 1.56)

Model 1: multinomial logistic regression adjusted for age, sex, and race. Model 2: as model 1, plus additional adjustment for education, smoking, body mass index, diabetes mellitus, hypertension, alcohol intake, and *APOE* genotype. Model 3: as model 2, plus additional adjustment for coronary heart disease, heart failure, and stroke. Model 4: as model 2, but restricted to participants without past history of stroke. AD indicates Alzheimer's disease; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; MCI, mild cognitive impairment.

MCI/dementia, but not with AD-related MCI/dementia (Table 2, models 3 and 4).

Correlates of MCI and Dementia in Persons with AF

Characteristics of the 611 persons with AF by MCI/dementia diagnosis are presented in Table 3, whereas Table S1 reports age-, sex-, and race-adjusted associations of participant characteristics with a diagnosis of MCI and dementia. Older age, being black, having a lower BMI, diabetes mellitus, stroke, higher CHA_2DS_2-VASc score, higher concentrations of N-terminal prohormone of B-type natriuretic peptide and troponin T, and presence of the *APOE* ε4 allele were all significantly associated with higher odds of dementia prevalence, whereas older age, male sex, and higher heart rate were associated with MCI prevalence. Prevalence of combined MCI/dementia increased monotonically with higher CHA_2DS_2-VASc, but not with HAS-BLED scores (Figure A). After multivariable adjustment, older age, lower BMI, diabetes mellitus, stroke, and presence of *APOE* ε4 allele remained associated with dementia prevalence, and male sex and higher heart rate with MCI prevalence (Table 4).

Table 3. Characteristics of Study Participants With AF by Cognitive Status, ARIC 2011 to 2013 (N=611)

	Normal	MCI	Dementia
N	374	169	68
Age, y	78 (5)	79 (5)	81 (5)
Women, %	49	38	51
Blacks, %	13	8	22
>High school, %	39	44	29
Alcohol intake, g/w	31 (65)	42 (80)	11 (42)
Current smoker, %	6	4	8
BMI, kg/m^2	29 (6)	30 (6)	27 (5)
Hypertension, %	79	79	74
Diabetes mellitus, %	38	44	62
Heart failure, %	25	26	31
Coronary heart disease, %	31	30	38
Stroke, %	8	10	21
Anticoagulant use, %	53	60	43
CHA_2DS_2-VASc	4.2 (1.5)	4.2 (1.4)	4.9 (1.7)
HAS-BLED	2.8 (0.7)	2.8 (0.8)	2.8 (0.8)
Heart rate, bpm	65 (13)	68 (13)	68 (12)
eGFR, mL/min per 1.73 m^2	59 (18)	57 (20)	55 (19)
NT-proBNP*	489 (185, 1140)	769 (275, 1415)	713 (302, 1657)
hs-CRP*	3.0 (1.6, 5.4)	2.5 (1.3, 6.1)	2.2 (1.1, 5.4)
Troponin T*	1.5 (1.0, 2.3)	1.7 (1.1, 2.7)	2.1 (1.3, 3.2)
APOE ε4 allele, %	25	25	41
Ejection fraction, %	62 (9)	60 (10)	60 (11)
LVMI, g per m^2	90 (26)	95 (28)	96 (35)
LAVI, mL per m^2	36 (16)	37 (17)	35 (13)
WMH volume, cm^3	19 (20)	21 (19)	31 (26)
Brain infarct, %	26	31	58
Microhemorrhage, %	27	29	42

Values correspond to mean (SD) or percent, unless otherwise stated. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; LAVI, left atrial volume index; LVMI, left ventricular mass index; MCI, mild cognitive impairment; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; WMH, white matter hyperintensities.
*Median (25th percentile, 75% percentile).

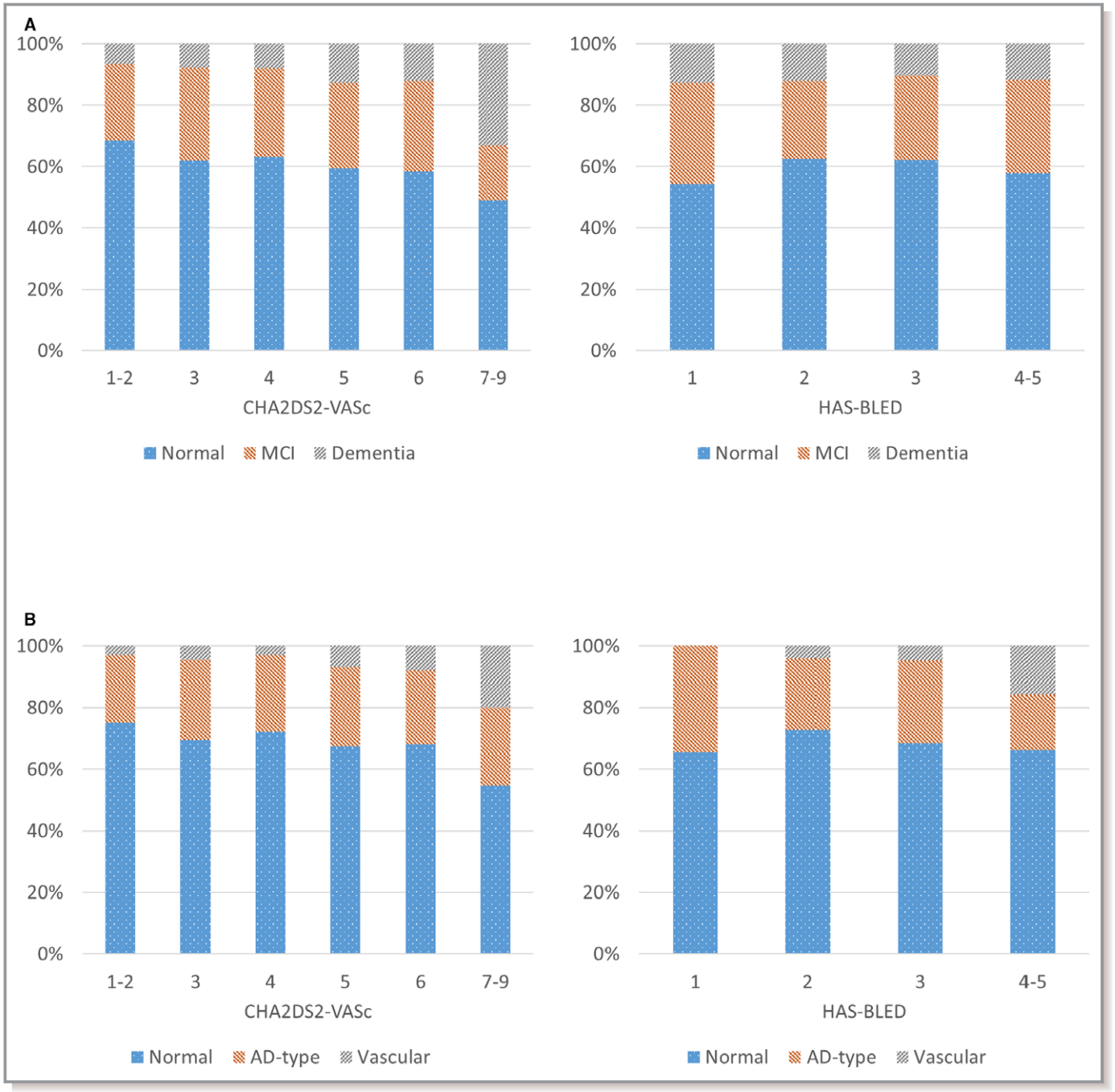

Figure. Prevalence of mild cognitive impairment or dementia (A) and by etiological diagnosis (B) across categories of CHA2DS2-VASc and HAS-BLED scores in persons with AF, ARIC cohort, 2011 to 2013. AD indicates Alzheimer's disease; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; MCI, mild cognitive impairment.

Correlates of AD-Related and Vascular MCI/Dementia in Persons With AF

Among the 611 participants with AF, 535 were considered cognitively normal or received a primary etiological diagnosis of AD-related or vascular MCI/dementia (76 participants had other etiologies as primary diagnosis or did not have enough information to make an etiological diagnosis). Primary AD-related MCI/dementia was diagnosed in 133 (24.9%) whereas primary vascular MCI/dementia was diagnosed in 32 (6.0%). Age-, sex-, and race-adjusted predictors of AD-related and vascular MCI/dementia are presented in Table S2. Only older age and diabetes mellitus were significantly associated with higher odds of AD-related MCI/dementia, whereas male sex, stroke, higher CHA_2DS_2-VASc and HAS-BLED scores, higher heart rate, lower kidney function, higher troponin T, and

Table 4. Correlates of MCI and Dementia Among Individuals With AF, ARIC Study, 2011 to 2013

	MCI	Dementia
	Odds Ratios (95% CIs)	
Age, per 5 y	1.17 (0.96, 1.42)	1.35 (1.01, 1.81)
Women (vs men)	0.80 (0.65, 0.98)	1.09 (0.81, 1.47)
Blacks (vs white)	0.80 (0.58, 1.12)	1.35 (0.93, 1.95)
BMI, per 5 kg/m^2	1.12 (0.93, 1.33)	0.60 (0.43, 0.84)
Diabetes mellitus	1.20 (0.79, 1.80)	3.41 (1.80, 6.49)
Stroke	1.03 (0.54, 1.98)	2.39 (1.10, 5.18)
Heart rate, per 10 beats per min	1.19 (1.02, 1.38)	1.11 (0.87, 1.43)
NT-proBNP, per doubling	1.10 (0.97, 1.24)	1.10 (0.91, 1.33)
Troponin T, per doubling	0.98 (0.78, 1.24)	1.26 (0.89, 1.78)
APOE ε4 allele	1.12 (0.71, 1.79)	2.35 (1.27, 4.37)

Results correspond to odds ratios (OR) and 95% CI of MCI and dementia from a multinomial logistic regression model including all the variables in the table. OR and 95% CI calculated from multinomial logistic regression adjusted for all covariates in the table. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; MCI, mild cognitive impairment; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide.

Table 5. Correlates of AD-Related MCI/Dementia and Vascular MCI/Dementia Among Individuals With AF, ARIC study, 2011 to 2013

	AD-Related MCI/Dementia	Vascular MCI/Dementia
	Odds Ratios (95% CIs)	
Age, per 5 y	1.21 (0.98, 1.48)	1.09 (0.74, 1.61)
Women (vs men)	0.89 (0.71, 1.12)	0.63 (0.40, 0.99)
Blacks (vs white)	1.00 (0.73, 1.36)	1.25 (0.72, 2.16)
Diabetes mellitus	1.66 (1.09, 2.51)	1.31 (0.56, 3.07)
Stroke	0.70 (0.32, 1.53)	9.95 (4.26, 23.3)
Heart rate, per 10 beats per min	1.12 (0.96, 1.31)	1.32 (0.97, 1.80)
eGFR, per 20 mL/min per 1.73 m^2 increase	1.08 (0.83, 1.41)	0.63 (0.37, 1.07)
Troponin T, per doubling	1.11 (0.84, 1.48)	0.92 (0.50, 1.67)
LVMI, per 30 g/m^2	1.03 (0.79, 1.33)	1.36 (0.87, 2.13)

Results correspond to odds ratios (OR) and 95% confidence intervals (CI) of AD-related MCI/dementia and vascular MCI/dementia from a multinomial logistic regression model including all the variables in the table. OR and 95% CI calculated from multinomial logistic regression adjusted for all covariates in the table. AD indicates Alzheimer's disease; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MCI, mild cognitive impairment.

higher LV mass index were significantly associated with higher odds of vascular MCI/dementia. As shown in Figure B, prevalence of vascular MCI/dementia monotonically increased with increasing CHA_2DS_2-VASc and HAS-BLED scores; no such trend was evident for AD-related MCI/dementia. In multivariable analysis, diabetes mellitus remained significantly associated with AD-related MCI/dementia (OR, 1.66; 95% CI, 1.09, 2.51), and male sex (OR, 1.60; 95% CI, 1.01, 2.53) and stroke (OR, 9.95; 95% CI, 4.26, 23.3) with vascular MCI/dementia (Table 5).

MRI Correlates of Dementia and MCI

Finally, we explored whether selected imaging markers of cerebrovascular disease were associated with MCI and dementia in 133 participants with AF who underwent brain MRI (Table 6). A doubling in the volume of white matter hyperintensities was associated with higher odds of combined MCI/dementia, particularly vascular MCI/dementia, whereas presence of infarcts was associated with higher odds of dementia. All patients with vascular MCI/dementia had at least 1 infarct. In this small sample, presence of microhemorrhages was not significantly associated with MCI or dementia. We also explored the association of the CHA_2DS_2-VASc score with the volume of white matter hyperintensities and prevalence of infarcts and microhemorrhages (Table 7). A 1-point increase in CHA_2DS_2-VASc was associated with 14% higher volume of white matter hyperintensities and 47% increased odds of prevalence of infarcts, but not with prevalence of microhemorrhages.

Discussion

In this analysis of a large cohort of elderly individuals with AF with detailed neurocognitive assessments and expert adjudication of MCI and dementia, we made the following observations: (1) Approximately 40% of people with AF were diagnosed with MCI or dementia; (2) odds of dementia and MCI were double and 20% higher, respectively, among individuals with AF compared with those without AF, even after adjustment for multiple potential confounders and mediators; and (3) key correlates of MCI and dementia among persons with AF were older age, diabetes mellitus (particularly for AD-related MCI/dementia), and past stroke (for vascular MCI/dementia).

The observed high prevalence of MCI and dementia among elderly AF patients has important implications for the management of the arrhythmia. First, current AF treatment guidelines call for the involvement and engagement of patients in decisions about their disease management.[25,26] However, individuals with MCI and dementia are likely to face unique challenges in this process, which should be recognized by

Table 6. Association of Brain MRI Findings With Mild Cognitive Impairment and Dementia Among Individuals With AF, ARIC Study, 2011 to 2013

	MCI/dementia	MCI	Dementia	AD-Related MCI/Dementia	Vascular MCI/Dementia
Odds ratios (95% CIs)					
WMH volume, per doubling	1.45 (1.02, 2.05)	1.42 (0.99, 2.04)	1.51 (0.81, 2.81)	1.31 (0.91, 1.88)	2.49 (1.22, 5.07)
Infarct	1.72 (0.78, 3.81)	1.41 (0.61, 3.26)	3.83 (1.02, 14.3)	0.98 (0.40, 2.41)	NA*
Microhemorrhage	1.26 (0.58, 2.77)	1.14 (0.50, 2.62)	1.84 (0.49, 6.84)	0.99 (0.42, 2.34)	3.63 (0.95, 13.9)

Results correspond to odds ratios and 95% confidence intervals from logistic regression models adjusted for age, sex, and race. AD indicates Alzheimer's disease; AF, atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NA, not applicable; WMH, white matter hyperintensities.
*All had infarcts.

clinicians and caregivers. AF guidelines, unfortunately, fail to address these issues (other than recommending the avoidance of oral anticoagulation in patients with dementia whose compliance cannot be ensured by a caregiver).[25,26] Second, identifying effective strategies that slow cognitive decline and prevent dementia in patients with AF is of paramount importance to improve outcomes in these patients.

Numerous studies, including our previous work in the ARIC cohort, have shown that individuals with AF experience faster cognitive decline and higher rates of dementia.[2,3,27,28] The higher rates of stroke in AF patients are certain to play a role, but other potential mechanisms have been proposed, including the development of silent cerebral infarcts or microhemorrhages, cerebral hypoperfusion, and the overall proinflammatory state associated with AF.[29] Our current results confirm the association between AF and dementia and, in addition, indicate that AF may be associated with an increased prevalence of MCI. Moreover, AF was not only associated with higher prevalence of vascular MCI/dementia, but also with a 20% to 30% increased odds of AD-related MCI/dementia. Though AF is unlikely to be directly involved in the pathogenesis of AD, AF-related processes may influence brain injury mechanisms that contribute to the development of AD-related MCI/dementia.

Table 7. Association of CHA2DS2-VASc Score With Brain MRI Findings Among Individuals With AF, ARIC study, 2011 to 2013

	Per 1-Point Increase in CHA_2DS_2-VASc	
	Relative Increase	*P* Value
White matter hyperintensities	14% (3%, 26%)	0.01
	OR (95% CI)	*P* value
Infarct	1.47 (1.11, 1.94)	0.007
Microhemorrhage	1.12 (0.86, 1.46)	0.40

Linear model (for white matter hyperintensities) and logistic model (infarct and hemorrhages) adjusted for race and including CHA_2DS_2-VASc as a continuous variable. AF indicates atrial fibrillation; ARIC, Atherosclerosis Risk in Communities; MRI, magnetic resonance imaging; OR, odds ratio.1

Not surprisingly, we found past history of stroke to be a strong predictor of vascular MCI/dementia. In contrast, some cardiovascular risk factors, such as hypertension, were only weakly associated with MCI or dementia. Diabetes mellitus, though, was an exception, showing a moderately strong association with overall dementia, particularly AD-related dementia. This observation is consistent with previous studies and meta-analyses[30] and underscores the need for adequate management of cardiometabolic risk factors in patients with AF. We also observed a lower prevalence of dementia with higher BMI, but this result is most likely attributed to reverse causation and adjustment for mediators such as diabetes mellitus.

Our analysis has several important strengths, including the careful and detailed cognitive phenotyping, expert adjudication of dementia and MCI diagnoses, availability of an etiological diagnosis for individuals with MCI or dementia, relatively large sample size, and diverse population, which facilitates generalizability of our findings. Nonetheless, the cross-sectional design, which may lead to survival bias, and the limited number of events in some etiological subgroups (such as vascular MCI/dementia) are limitations to be noted. Our findings have to be interpreted with caution given the large number of tests and comparisons we ran, which may have resulted in some associations being false positives. In addition, the clinical diagnosis of AD-related MCI/dementia may have incorrectly categorized some participants with other etiologies (eg, vascular), which could explain the observed association between AF and AD-related MCI/dementia. Finally, we did not explicitly test whether correlates of MCI/dementia were different in persons with AF compared with those without AF because statistical power of such analysis would have been limited.

In conclusion, we corroborated the association of AF with higher prevalence of MCI and dementia, found that elderly patients with AF experience a high burden of MCI and dementia, and identified correlates of MCI/dementia in this

population. Our findings underscore the importance of considering cognitive function in the management of patients with AF and the urgent need to develop evidence-based strategies aimed to prevent cognitive decline and improve cognitive outcomes among this patient population.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Correlates of mild cognitive impairment (MCI) and dementia among individuals with atrial fibrillation, ARIC study, 2011-2013. Results correspond to odds ratios (OR) and 95% confidence intervals (CI) of MCI and dementia from a multinomial logistic regression model adjusted for age, sex, and race

	MCI	Dementia
	Odds ratios (95% confidence intervals)	
Age, per 5 years	1.18 (1.00, 1.41)	1.65 (1.27, 2.14)
Women (vs men)	0.81 (0.67, 0.98)	0.99 (0.76, 1.29)
African Americans (vs white)	0.84 (0.61, 1.15)	1.44 (1.03, 2.02)
Education		
< High school	1 (ref.)	1 (ref.)
Completed high school	1.12 (0.85, 1.48)	0.95 (0.66, 1.37)
At least some college	1.19 (0.90, 1.57)	0.70 (0.48, 1.04)
Alcohol intake, per 1 drink/day	1.18 (0.91, 1.54)	0.49 (0.19, 1.25)
Smoking		
Never	1 (ref.)	1 (ref.)
Former	0.97 (0.67, 1.40)	1.01 (0.62, 1.63)
Current	0.77 (0.40, 1.48)	1.24 (0.57, 2.68)
BMI, per 5 kg/m^2	1.15 (0.97, 1.36)	0.73 (0.54, 0.99)
Hypertension	1.03 (0.65, 1.64)	0.72 (0.38, 1.37)
Diabetes	1.33 (0.91, 1.94)	2.64 (1.49, 4.69)
Heart failure	1.02 (0.66, 1.56)	1.25 (0.70, 2.24)
Coronary heart disease	0.85 (0.57, 1.28)	1.21 (0.69, 2.11)
Stroke	1.17 (0.62, 2.22)	2.88 (1.41, 5.88)
Anticoagulant use	1.29 (0.88, 1.88)	0.69 (0.40, 1.18)
CHA2DS2-VASc, per 1-point	1.02 (0.89, 1.17)	1.29 (1.07, 1.56)
HAS-BLED, per 1-point	1.08 (0.85, 1.37)	0.94 (0.66, 1.33)
Heart rate, per 10 beats per min	1.22 (1.05, 1.42)	1.16 (0.94, 1.44)
eGFR, per 20 mL/min/1.73 m^2 increase	0.94 (0.77, 1.16)	0.93 (0.68, 1.27)
NT-proBNP, per doubling	1.12 (1.01, 1.25)	1.19 (1.02, 1.40)
hs-CRP, per doubling	1.00 (0.89, 1.12)	0.93 (0.78, 1.10)

Troponin T, per doubling	1.11 (0.90, 1.36)	1.43 (1.08, 1.89)
APOE ε4 allele	1.02 (0.65, 1.60)	2.02 (1.13, 3.61)
Ejection fraction, per 10% decrease	1.19 (0.97, 1.46)	1.26 (0.95, 1.68)
LVMI, per 30 g/m^2	1.14 (0.93, 1.40)	1.27 (0.92, 1.75)
LAVI, per 15 mL/m^2	1.01 (0.85, 1.20)	0.91 (0.66, 1.25)
OR and 95%CI calculated from multinomial logistic regression adjusted for age, sex, and race		

Table S2. Correlates of Alzheimer's disease (AD)-related mild cognitive impairment (MCI)/dementia and vascular MCI/dementia among individuals with atrial fibrillation, ARIC study, 2011-2013. Results correspond to odds ratios (OR) and 95% confidence intervals (CI) of AD-related MCI/dementia and vascular MCI/dementia from a multinomial logistic regression model adjusted for age, sex, and race.

	AD-related MCI/dementia	Vascular MCI/dementia
	Odds ratios (95% confidence intervals)	
Age, per 5 years	1.23 (1.02, 1.48)	1.15 (0.82, 1.62)
Women (vs men)	0.74 (0.49, 1.11)	0.43 (0.20, 0.95)
African Americans (vs white)	1.10 (0.60, 2.02)	1.95 (0.75, 5.12)
Education		
< High school	1 (ref.)	1 (ref.)
Completed high school	1.32 (0.72, 2.44)	0.51 (0.17, 1.55)
At least some college	1.06 (0.57, 1.99)	1.15 (0.43, 3.05)
Alcohol intake, per 1 drink/day	0.97 (0.70, 1.34)	1.08 (0.63, 1.84)
Smoking		
Never	1 (ref.)	1 (ref.)
Former	0.98 (0.65, 1.46)	1.11 (0.58, 2.14)
Current	0.84 (0.42, 1.67)	1.29 (0.45, 3.70)
BMI, per 5 kg/m^2	1.00 (0.83, 1.21)	1.11 (0.79, 1.55)
Hypertension	0.89 (0.55, 1.45)	0.74 (0.32, 1.75)
Diabetes	1.69 (1.12, 2.54)	1.95 (0.91, 4.17)
Heart failure	1.02 (0.65, 1.62)	1.84 (0.86, 3.92)
Coronary heart disease	0.98 (0.64, 1.52)	1.18 (0.55, 2.53)
Stroke	0.80 (0.37, 1.74)	11.2 (5.01, 24.9)
Anticoagulant use	1.16 (0.77, 1.73)	1.44 (0.68, 3.06)
CHA_2DS_2-VASc, per 1-point	1.02 (0.88, 1.18)	1.60 (1.25, 2.03)
HAS-BLED, per 1-point	0.94 (0.72, 1.23)	2.50 (1.51, 4.12)
Heart rate, per 10 beats per min	1.14 (0.97, 1.33)	1.34 (1.02, 1.75)
eGFR, per 20 mL/min/1.73 m^2 increase	1.02 (0.81, 1.28)	0.59 (0.39, 0.88)
NT-proBNP, per doubling	1.11 (0.98, 1.25)	1.18 (0.94, 1.47)

hs-CRP, per doubling	0.91 (0.79, 1.03)	1.15 (0.91, 1.46)
Troponin T, per doubling	1.12 (0.88, 1.41)	1.51 (1.02, 2.25)
APOE ε4 allele	1.47 (0.93, 2.32)	1.62 (0.74, 3.56)
Ejection fraction, per 10% decrease	1.23 (0.99, 1.53)	1.18 (0.79, 1.77)
LVMI, per 30 g/m^2	1.09 (0.86, 1.38)	1.43 (1.01, 2.03)
LAVI, per 15 mL/m^2	0.96 (0.79, 1.17)	1.13 (0.88, 1.45)
OR and 95%CI calculated from multinomial logistic regression adjusted for age, sex, and race		