JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 9, 2019

PUBLISHED BY ELSEVIER

ORIGINAL INVESTIGATIONS

Relationships of Overt and Silent Brain Lesions With Cognitive Function in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Patients with atrial fibrillation (AF) have an increased risk of cognitive decline, potentially resulting from clinically unrecognized vascular brain lesions.

OBJECTIVES This study sought to assess the relationships between cognitive function and vascular brain lesions in patients with AF.

METHODS Patients with known AF were enrolled in a multicenter study in Switzerland. Brain magnetic resonance imaging (MRI) and cognitive testing using the Montreal Cognitive Assessment (MoCA) were performed in all participants. Large noncortical or cortical infarcts (LNCCIs), small noncortical infarcts (SNCIs), microbleeds, and white matter lesions were quantified by a central core laboratory. Clinically silent infarcts were defined as infarcts on brain MRI in patients without a clinical history of stroke or transient ischemic attack.

RESULTS The study included 1,737 patients with a mean age of 73 ± 8 years (28% women, 90% taking oral anticoagulant agents). On MRI, LNCCIs were found in 387 patients (22%), SNCIs in 368 (21%), microbleeds in 372 (22%), and white matter lesions in 1715 (99%). Clinically silent infarcts among the 1,390 patients without a history of stroke or transient ischemic attack were found in 201 patients with LNCCIs (15%) and 245 patients with SNCIs (18%). The MoCA score was 24.7 ± 3.3 in patients with and 25.8 ± 2.9 in those without LNCCIs on brain MRI ($p < 0.001$). The difference in MoCA score remained similar when only clinically silent LNCCIs were considered (24.9 ± 3.1 vs. 25.8 ± 2.9; $p < 0.001$). In a multivariable regression model including all vascular brain lesion parameters, LNCCI volume was the strongest predictor of a reduced MoCA ($\beta = -0.26$; 95% confidence interval: −0.40 to −0.13; $p < 0.001$).

CONCLUSIONS Patients with AF have a high burden of LNCCIs and other brain lesions on systematic brain MRI screening, and most of these lesions are clinically silent. LNCCIs were associated with worse cognitive function, even among patients with clinically silent infarcts. Our findings raise the question of MRI screening in patients with AF. (J Am Coll Cardiol 2019;73:989-99) © 2019 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.12.039

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

FLAIR = fluid-attenuated inversion recovery

LNCCI = large noncortical or cortical infarct

MoCA = Montreal Cognitive Assessment

MRI = magnetic resonance imaging

SNCI = small noncortical infarct

TIA = transient ischemic attack

The prevalence of atrial fibrillation (AF) in the general population is increasing rapidly (1). Patients with AF are at high risk of adverse events. Although the relationships of AF with death, stroke, and congestive heart failure have been known for many years (2,3), more recent evidence suggests that patients with AF also face an increased risk of cognitive dysfunction and dementia (4,5). This growing awareness is reflected by a recent publication of an international expert consensus paper on this topic (6).

Meta-analyses suggest that part of the association between AF and dementia is explained by the higher stroke risk among patients with AF, but the risk of dementia was also increased in patients with AF but without a clinical history of stroke (5). Clinically unrecognized (silent) cerebral infarcts, microbleeds, or other brain lesions may explain this association, but systematic investigations in patients with AF are currently lacking. Microbleeds are of particular interest because patients with AF usually need lifelong oral anticoagulation for stroke prevention (7). Although prior studies did not show a consistent trend of more microbleeds among patients using oral anticoagulation, the use of this therapy among patients with a significant burden of microbleeds remains controversial (8–10).

The aim of the current study was to assess the relationships of clinically known and unknown (silent) vascular brain lesions detected on brain magnetic resonance imaging (MRI) with cognitive function in a large sample of patients with AF. We focused on large infarcts and infarcts involving the brain cortex, which may originate from embolic mechanisms and as such represent AF-related sequelae. We also considered imaging markers of cerebral small vessel disease, which share vascular risk factors with AF, including white matter disease, small noncortical infarcts

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Manuscript received September 13, 2018; revised manuscript received November 14, 2018, accepted December 3, 2018.

(SNCIs), and microbleeds (11). Both cerebral small vessel disease and embolic stroke are key mechanisms underlying the development of vascular dementia (12).

METHODS

STUDY DESIGN AND PARTICIPANTS. The Swiss-AF (Swiss Atrial Fibrillation) study is an ongoing prospective cohort study that enrolled 2,415 patients between 2014 and 2017 across 14 centers in Switzerland. The detailed methodology has been described previously (13). Patients were eligible for Swiss-AF if they had a history of documented AF and if they were 65 years old or older. In addition, we aimed to enroll 10% to 15% of patients between 45 and 65 years of age to assess the effects of AF on individuals in the active workforce. We excluded patients with secondary forms of AF and patients who were unable to provide informed consent. Patients with an acute illness within the last 4 weeks could be enrolled only once the acute episode had resolved.

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Of the 2,415 patients enrolled in Swiss-AF, 667 did not have a brain MRI at baseline. The main reason for a missing brain MRI was the presence of a cardiac device (n = 461; 69%). Other reasons included further contraindications to perform an MRI or claustrophobia of the patient. An additional 11 patients did not undergo cognitive testing, thus leaving 1,737 participants for the present analysis. The local ethics committees approved the study protocol, and written informed consent was obtained from all participants.

CLINICAL MEASURES. Information on personal characteristics, risk factors, comorbidities, antithrombotic treatment, and other factors was obtained through standardized case report forms. Weight and height were directly measured, and body mass index was calculated as weight in kilograms divided by height in meters squared. At baseline, 3 consecutive blood pressure measurements were obtained, and the mean of them was used in all analyses. We classified AF into paroxysmal, persistent, and permanent AF according to recommended definitions (7).

BRAIN MAGNETIC RESONANCE IMAGING. Brain MRI was acquired on a 1.5-T or 3.0-T scanner. The standardized protocol included a 3-dimensional T_1-weighted magnetization-prepared rapid gradient echo (MPRAGE) (spatial resolution 1.0 × 1.0 × 1.0 mm^3), a 2-dimensional axial fluid-attenuated inversion recovery (FLAIR) (spatial resolution 1.0 × 1.0 × 3.0 mm^3), and 2-dimensional axial diffusion-weighted imaging (spatial resolution 1.0 × 1.0 × 3.0 mm^3) sequence with whole brain coverage and without interpolation. In addition, either a 2-dimensional axial susceptibility-weighted imaging (spatial resolution 1.0 × 1.0 × 3.0 mm^3) or a 2-dimensional axial T_2*-weighted (spatial resolution of 1.0 × 1.0 × 3.0 mm^3) sequence was applied.

All brain MRI scans were analyzed centrally in a specialized imaging core laboratory (Medical Image Analysis Centre, Basel, Switzerland). MRI scans were analyzed by blinded expert raters unaware of personal characteristics or cognitive function. They marked and segmented lesions in a standardized fashion using an in-house procedure approved for international clinical studies. Board-certified neuroradiologists confirmed all ratings. SNCIs were defined as hyperintense lesions on FLAIR ≤20 mm in diameter on axial sections and not involving the cortex, consistent with ischemic infarction in the territory of a perforating arteriole (located in the white matter, internal or external capsule, deep brain nuclei, thalamus, or brainstem) (11). We did not further differentiate between SNCIs and lacunes on the basis of the presence or absence of a central fluid-filled cavity. Large noncortical infarcts were noncortical infarcts with a diameter >20 mm. Cortical infarcts were defined as hyperintense lesions on FLAIR involving the cortex irrespective of their size and whether or not they also involved subcortical areas.

For the present analysis we differentiated between SNCIs and large noncortical infarcts or cortical infarcts (LNCCIs). Hyperintense white matter lesions were graded using the Fazekas scale, and at least moderate disease was defined as a score ≥2 in either the periventricular or the deep white matter region (14). Perivascular spaces were identified, differentiated by their tubular morphology, and subsequently excluded. FLAIR-hyperintense lesions not meeting the criteria mentioned earlier were identified as white matter lesions. Microbleeds were identified and counted as nodular, strongly hypointense lesions on either T_2*-weighted or susceptibility-weighted imaging. T_2-weighted volumes of noncortical and cortical infarcts as well as white matter lesions were segmented and quantified semiautomatically using Amira (Mercury Computer Systems Inc., Chelmsford, Massachusetts). Lesions with a central FLAIR-hypointense core were segmented in total without differentiating between hyperintense and hypointense lesion areas.

COGNITIVE TESTING. All study personnel were centrally trained to perform a standardized neurocognitive assessment. The Montreal Cognitive

Assessment (MoCA) evaluates visuospatial and executive functions, confrontation naming, memory, attention, language, and abstraction (15). Patients can obtain a maximum of 30 points, with higher scores indicating better cognitive function. One point was added to the total test score if the patient had 12 years or less of formal education.

STATISTICAL ANALYSIS. Baseline characteristics were stratified by the presence or absence of a clinical history of stroke or transient ischemic attack (TIA) and presented as mean ± SD for continuous variables or as counts (percentages) for nominal variables. We compared differences across groups with Wilcoxon rank sum tests or chi-square tests, as appropriate. Silent cerebral infarcts were defined as cerebral infarcts (LNCCIs or SNCIs) on brain MRI in patients without a history of stroke or TIA. Lesion volumes were indicated as median (interquartile range) given their skewed distribution.

Given that history of stroke or TIA is a key predictor of lower cognitive function, we repeated all main analyses in patients without a history of stroke or TIA. To assess the associations of vascular brain lesion parameters with MoCA score values and to adjust for potential confounders, we constructed linear mixed effects regression models in which study center was included as a random intercept to account for potential differences across study centers. We first fitted univariable models using log-transformed and centered vascular brain lesion parameters (or counts for microbleeds) as MoCA score predictors. Separate models were constructed for each brain lesion parameter. Univariable models were adjusted for a pre-defined set of covariates, including age, sex, body mass index, education level, smoking status, history of hypertension, history of diabetes, AF type, and use of oral anticoagulation. Finally, we constructed a combined multivariable model including all structural brain lesion parameters in a single model. We performed 2 sensitivity analyses, 1 that additionally adjusted the combined model for a history of cardioversion or left atrial ablation and 1 adjusting for time since first AF diagnosis. Finally, to examine the independence of SNCI and LNCCI, we performed 2 additional analyses in which we excluded patients who had both SNCIs and LNCIs on brain MRI.

MoCA scores were compared across different strata and subgroups by using likelihood ratio tests between mixed effects models with and without the stratum as single predictor. In all models, we included dummy indicators representing the presence or absence of each vascular brain lesion type, in addition to the actual volume or count measurement. Visual model diagnostics were performed, and no major violations of model assumptions of homogeneity and normally distributed residuals were detected. The microbleed count was truncated at 20, and 3 outliers were given a count of 20 to minimize their influence on the associations. All analyses were performed on an available data basis and conducted using R version 3.5.1 (R Core Team, 2018, R Foundation, Vienna, Austria); mixed effects models were constructed using the nlme package (16).

RESULTS

Baseline characteristics are shown in **Table 1**. Mean age was 73 ± 8 years, 28% of participants were women, 90% were anticoagulated at the time of study enrollment (54% direct oral anticoagulant agents, 36% vitamin K antagonists), and 18% were receiving antiplatelet therapy. Patients with a history of stroke or TIA were older, had a higher prevalence of hypertension and diabetes, and were more often taking oral anticoagulant agents.

Prevalence and size of vascular brain lesions detected on brain MRI are shown in **Table 2**. At least 1 LNCCI was detected in 22% of participants, with a median volume of 1,623 mm^3. SNCIs were observed in 21% (median volume 63 mm^3). The overlap between LNCCI and SNCI was small; 68% of patients with SNCIs had no LNCCIs, and 75% of patients with LNCCIs had no SNCIs, such that 30% of the study population had either LNCCIs or SNCIs. Microbleeds were observed in 22% (median count 1) and white matter lesions in 99% (median volume 3,918 mm^3). The extent of white matter lesions was at least moderate in 54% of participants. When patients with a history of stroke or TIA were excluded, 201 of 1,390 (15%) participants had evidence of a silent LNCCI (median volume 525 mm^3), and 245 (18%) had evidence of a silent SNCI (median volume 57 mm^3) (**Table 2**).

Comparisons of MoCA scores between patients with and without a specific vascular brain lesion are shown in **Figures 1A and 1B** and in Online Table 1. The least square mean MoCA was 24.9 (95% confidence interval [CI]: 24.3 to 25.5) and 25.9 (95% CI: 25.3 to 26.5) among patients with and without an LNCCI on brain MRI ($p < 0.001$). The MoCA was 25.0 (95% CI: 24.4 to 25.6) versus 25.9 (95% CI: 25.3 to 26.4) in patients with and without an SNCI ($p < 0.001$) and 25.4 (95% CI: 24.7 to 26.0) versus 25.8 (95% CI: 25.2 to 26.4) in patients with and without microbleeds ($p = 0.07$). When patients with a clinical history of stroke or TIA were excluded, the MoCA score difference between patients with or without silent LNCCI (25.1; 95% CI: 24.4 to 25.7 vs. 26.0; 95% CI: 25.4 to 26.5; $p < 0.001$),

TABLE 1 Baseline Characteristics

	All Patients (N = 1,737)	No History of Stroke/TIA (n = 1,390)	History of Stroke/TIA (n = 347)	p Value*
Age, yrs	73 ± 8	72 ± 9	75 ± 7	<0.001
Female	477 (28)	369 (27)	108 (31)	0.10
Body mass index, kg/m^2	27.7 ± 4.8	27.8 ± 4.8	27.3 ± 4.7	0.10
Blood pressure, mm Hg	135 ± 19/79 ± 12	135 ± 18/79 ± 12	135 ± 19/78 ± 12	0.69/0.12
History of hypertension	1,197 (69)	939 (68)	258 (74)	0.017
History of diabetes mellitus	265 (15)	197 (14)	68 (20)	0.015
Smoking status				0.73
Current	168 (10)	138 (10)	30 (9)	
Past	871 (50)	697 (50)	174 (50)	
Never	695 (40)	552 (40)	143 (41)	
Education level†				0.43
Basic	203 (12)	157 (11)	46 (13)	
Middle	850 (49)	677 (49)	173 (50)	
Advanced	684 (39)	556 (40)	128 (37)	
Atrial fibrillation type				0.012
Paroxysmal	797 (46)	623 (45)	174 (50)	
Persistent	524 (30)	442 (32)	82 (24)	
Permanent	416 (24)	325 (23)	91 (26)	
History of coronary artery disease	462 (27)	363 (26)	99 (29)	0.40
History of clinical stroke	230 (13)	0 (0)	230 (66)	–
History of TIA	159 (9)	0 (0)	159 (46)	–
History of heart failure	376 (22)	295 (21)	81 (23)	0.44
History of major bleeding	97 (6)	72 (5)	25 (7)	0.18
CHA_2DS_2-VASc score	3.3 ± 1.7	2.8 ± 1.4	5.3 ± 1.3	<0.001
Oral anticoagulation	1,560 (90)	1,236 (89)	324 (93)	0.019
Direct oral anticoagulants	929 (54)	741 (53)	188 (54)	0.82
Vitamin K antagonists	631 (36)	495 (36)	136 (39)	0.24
Antiplatelet therapy	309 (18)	237 (17)	72 (21)	0.12

Values are mean ± SD or n (%). *The p value compares patients with and without a history of stroke or TIA; p values were obtained from Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables. †Basic education: ≤6 yrs (less than compulsory education curriculum); middle education: 6 to ≤12 yrs (high school or similar); advanced education: ≥12 yrs (college or university degree).

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 yrs (2 points), diabetes, prior stroke or TIA or thromboembolism (2 points), vascular disease, age 65 to 74 yrs, female sex; TIA = transient ischemic attack.

with or without silent SNCI (25.1; 95% CI: 24.5 to 25.7 vs. 26.0; 95% CI: 25.4 to 26.5; p < 0.001), and with or without microbleeds (25.5; 95% CI: 24.9 to 26.2 vs. 25.9; 95% CI: 25.3 to 26.5; p = 0.15) remained of similar magnitude.

In univariable regression models, LNCCI volume on brain MRI was significantly related to MoCA scores, with larger infarct volumes predicting lower MoCA scores (β = −0.28; 95% CI: −0.42 to −0.13; p < 0.001) (Table 3). A similar finding was observed with white matter lesion volume (β = −0.38; 95% CI: −0.49 to −0.28; p < 0.001), and presence of at least moderate white matter lesions (β = −0.99; 95% CI: −1.27 to −0.72; p < 0.001). There was no significant association with SNCI volume or microbleed count. In multivariable models, LNCCI count and volume as well as presence of at least moderate white matter lesions (β = −0.40; 95% CI: −0.68 to −0.11; p = 0.007) remained strongly associated with lower MoCA scores

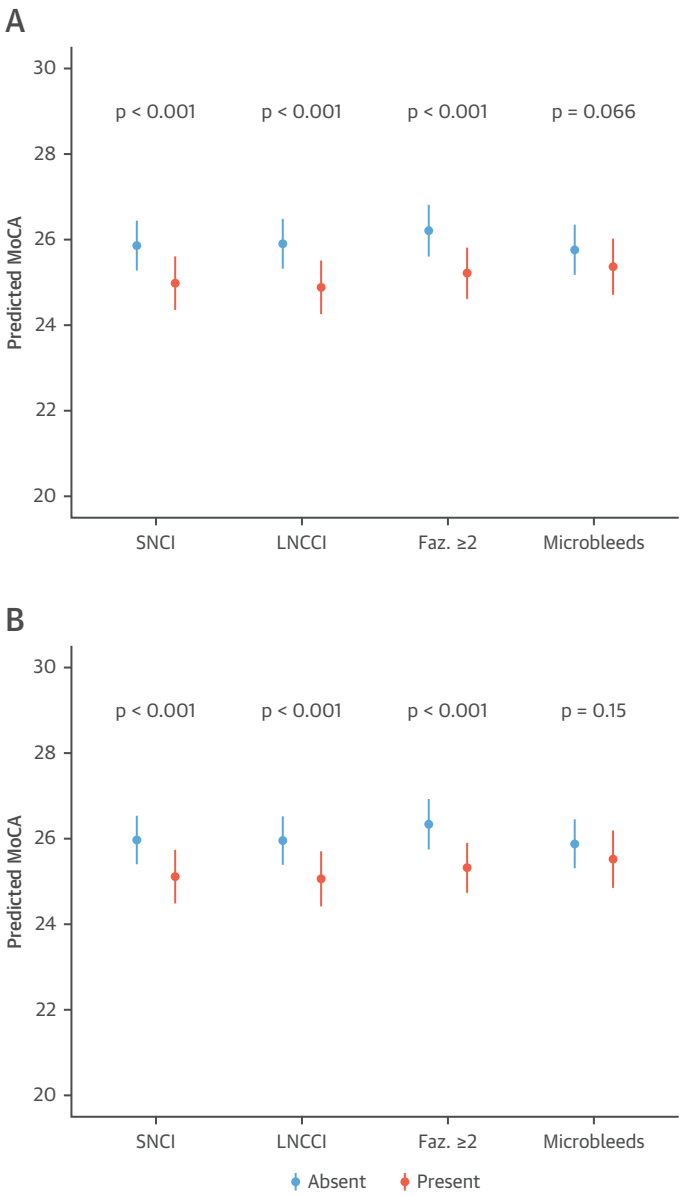
TABLE 2 Prevalence of Vascular Brain Lesions Detected on Brain Magnetic Resonance Imaging

	Prevalence	Volume, mm^3	Number
All patients (N = 1,737)			
Small noncortical infarcts	368 (21)	63 [30–163]	1 [1–3]
Large noncortical or cortical infarcts	387 (22)	1,623 [255–7,314]	1 [1–2]
Microbleeds	372 (22)	-	1 [1–2]
White matter lesions	1,715 (99)	3,918 [1,439–9783]	23 [11–41]
Fazekas scale ≥2	928 (54)		
Patients without a history of stroke or TIA (n = 1,390)			
Small noncortical infarcts	245 (18)	57 [30–141]	2 [1–3]
Large noncortical or cortical infarcts	201 (15)	525 [162–3,396]	1 [1–2]
Microbleeds	272 (20)	-	1 [1–2]
White matter lesions	1,372 (99)	3,512 [1,323–8,669]	21 [10–40]
Fazekas scale ≥2	694 (50)		

Values are n (%) or median [interquartile range].

TIA = transient ischemic attack.

FIGURE 1 Least Square Mean MoCA Score According to the Presence or Absence of a Specific Vascular Brain Abnormality



(A) All patients. **(B)** Patients without a history of stroke or transient ischemic attack. Least square means were obtained from linear mixed effects models that included covariates for the presence versus absence of a specific damage and damage volume (count for microbleeds), and study center as random intercept. Faz = Fazekas scale; LNCCI = large noncortical or cortical infarcts; MoCA = Montreal Cognitive Assessment; SNCI = small noncortical infarcts.

(**Table 3**). Coefficients of all covariates included in the multivariable models are presented in Online Table 2. In a combined multivariable model including all vascular brain lesion parameters, LNCCI count and volume were the strongest predictors of the MoCA score (**Table 3**, Online Table 3). When we excluded patients with a history of stroke or TIA, presence of LNCCI ($\beta = -0.53$; 95% Cl: −0.94 to −0.12; $p = 0.012$), LNCCI volume ($\beta = -0.18$; 95% Cl: −0.39 to 0.02; $p = 0.072$), and presence of at least moderate white matter lesions ($\beta = -0.46$; 95% CI: −0.77 to −0.16; $p = 0.003$) remained associated with the MoCA score (**Table 3**, Online Tables 4 and 5). Sensitivity analyses with models including covariates for a baseline history of cardioversion and left atrial ablation, or time since first AF diagnosis provided very similar results (Online Tables 6 to 9). Excluding patients with both SNCIs and LNCCIs on brain MRI also provided similar results (Online Tables 10 and 11).

Stratified MoCA score results are shown in **Figure 2**. The overall mean MoCA score was 25.5 ± 3.1. It was 24.7 ± 3 .7 and 25.6 ± 2.9 among patients with and without a clinical history of stroke ($p < 0.001$), respectively. MoCA scores also differed across strata of age, AF type, hypertension, diabetes, oral anticoagulation, and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years [2 points], diabetes, prior stroke or TIA or thromboembolism [2 points], vascular disease, age 65 to 74 years, female sex) score, but not sex. Patients with permanent AF had lower MoCA scores than patients with paroxysmal or persistent AF, a finding that persisted in multivariable models (Online Table 3).

The same subgroups were assessed for differences in brain lesion parameters (Online Table 12). Larger LNCCI volumes were observed in patients with permanent AF, higher CHA_2DS_2-VASc scores, and those with a history of stroke, hypertension, or diabetes. Oral anticoagulation with either direct oral anticoagulant agents or vitamin K antagonists was not associated with a higher microbleed count compared with no anticoagulation. Higher CHA_2DS_2-VASc scores were associated with significantly higher infarct and white matter lesion volumes, but lower microbleed counts (Online Table 12).

DISCUSSION

Several important findings emerged from this comprehensive analysis of vascular brain lesions and cognitive function in patients with AF (**Central Illustration**). First, participants had a substantial burden of vascular brain lesions detected on systematic brain MRI: 22% and 21% had evidence of a previous LNCCI and SNCI, respectively. Second, among patients without a history of stroke or TIA, 15% and 18% still had evidence of a previous clinically silent LNCCI and SNCI, respectively. Thus, most of the observed lesions were clinically silent. Third,

TABLE 3 Linear Mixed Effect Models Assessing the Relationships of MoCA Score With Vascular Brain Lesion Parameters

Predictor of Interest	Presence of Damage Type			Volume/Count		
	β Coefficient	95% CI	p Value	β Coefficient	95% CI	p Value
All patients						
Small noncortical infarcts						
Univariable	−0.87	(−1.22 to −0.53)	<0.001	−0.15	(−0.41 to 0.10)	0.24
Multivariable	−0.43	(−0.76 to −0.10)	0.010	−0.11	(−0.35 to 0.13)	0.38
Combined*	−0.32	(−0.67 to 0.03)	0.072	−0.15	(−0.39 to 0.10)	0.24
Large noncortical or cortical infarcts						
Univariable	−1.02	(−1.35 to −0.69)	<0.001	−0.28	(−0.42 to −0.13)	<0.001
Multivariable	−0.66	(−0.97 to −0.34)	<0.001	−0.26	(−0.39 to −0.12)	<0.001
Combined*	−0.64	(−0.97 to −0.31)	<0.001	−0.26	(−0.40 to −0.13)	<0.001
Microbleeds						
Univariable	−0.39	(−0.81 to 0.03)	0.07	0.03	(−0.09 to 0.14)	0.66
Multivariable	−0.03	(−0.42 to 0.36)	0.88	0.04	(−0.07 to 0.14)	0.52
Combined*	0.02	(−0.37 to 0.41)	0.93	0.08	(−0.03 to 0.19)	0.16
White matter lesions						
Univariable	−0.59	(−1.99 to 0.81)	0.41	−0.38	(−0.49 to −0.28)	<0.001
Multivariable	0.14	(−1.20 to 1.47)	0.84	−0.12	(−0.23 to −0.01)	0.028
Combined*	0.43	(−0.92 to 1.78)	0.53	−0.06	(−0.18 to 0.05)	0.29
Fazekas scale ≥2						
Univariable	−0.99	(−1.27 to −0.72)	<0.001			
Multivariable	−0.40	(−0.68 to −0.11)	0.007			
Patients without a history of stroke or TIA						
Small noncortical infarcts						
Univariable	−0.85	(−1.24 to −0.46)	<0.001	−0.16	(−0.48 to 0.16)	0.33
Multivariable	−0.44	(−0.82 to −0.07)	0.021	−0.09	(−0.39 to 0.21)	0.54
Combined†	−0.35	(−0.76 to 0.05)	0.09	−0.05	(−0.36 to 0.25)	0.74
Large noncortical or cortical infarcts						
Univariable	−0.90	(−1.32 to −0.48)	<0.001	−0.21	(−0.42 to −0.00)	0.06
Multivariable	−0.58	(−0.98 to −0.18)	0.004	−0.19	(−0.39 to 0.01)	0.06
Combined†	−0.53	(−0.94 to −0.12)	0.012	−0.18	(−0.39 to −0.02)	0.07
Microbleeds						
Univariable	−0.35	(−0.84 to 0.13)	0.15	−0.01	(−0.17 to 0.15)	0.93
Multivariable	0.02	(−0.43 to 0.48)	0.92	−0.01	(−0.16 to 0.14)	0.94
Combined†	0.06	(−0.40 to 0.52)	0.81	0.03	(−0.12 to 0.19)	0.66
White matter lesions						
Univariable	−0.58	(−2.05 to 0.89)	0.44	−0.35	(−0.46 to −0.24)	<0.001
Multivariable	0.14	(−1.26 to 1.54)	0.85	−0.10	(−0.22 to 0.02)	0.11
Combined†	0.41	(−1.03 to 1.85)	0.57	−0.04	(−0.17 to 0.09)	0.57
Fazekas scale ≥2						
Univariable	−1.01	(−1.31 to −0.72)	<0.001			
Multivariable	−0.46	(−0.77 to −0.16)	0.003			

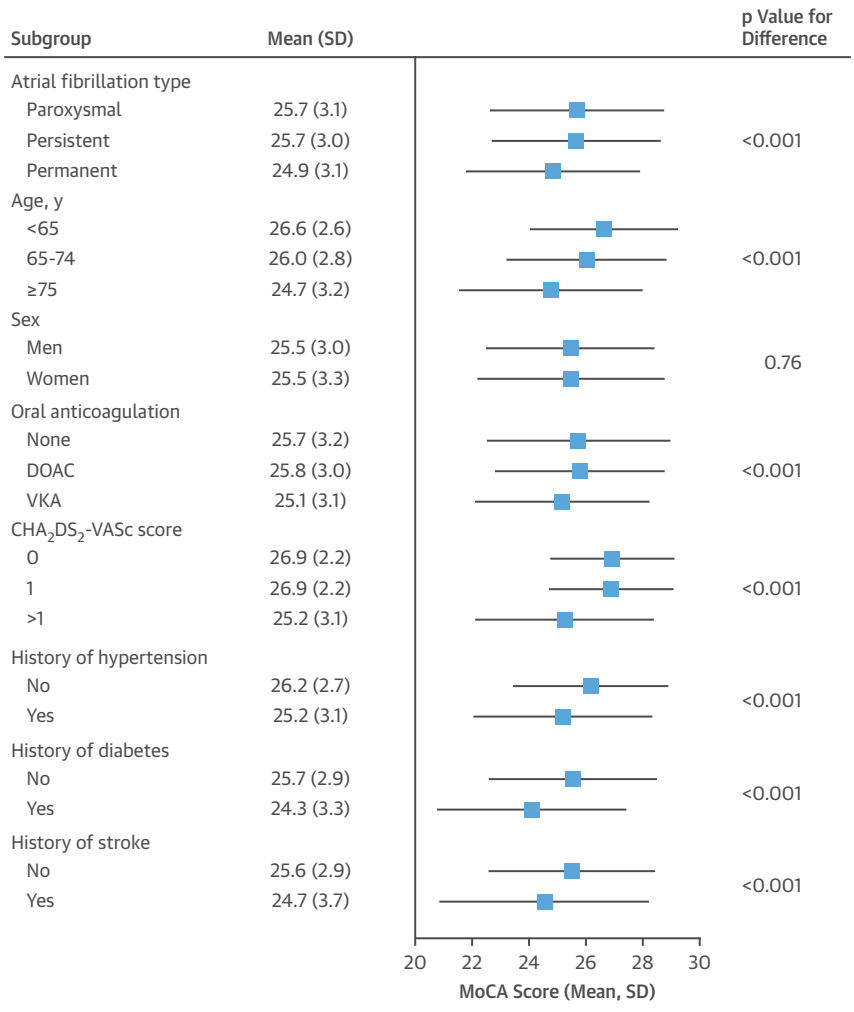
Results are from linear mixed effects models, taking into account the effect of study center. Vascular brain lesion volumes are centered on the mean natural-log transformed volumes. Models include, for each damage type, an indicator of the presence of the damage alongside the measurement of volume or, for microbleeds, count. Multivariable models are adjusted for age, sex, history of hypertension, smoking status, history of diabetes, body mass index, atrial fibrillation type, education level, oral anticoagulation (yes, no). Coefficients of all covariates are presented in Online Tables 2 and 4. The combined multivariable model includes all vascular brain lesion variables. Coefficients of all covariates from the combined model are presented in Online Tables 3 and 5. No. of patients with microbleeds = 1,682; No of patients with microbleeds without a history of stroke or TIA = 1,348. *The combined model included 1,677 patients. †The combined model included 1,344 patients.

CI = confidence interval; MoCA = Montreal Cognitive Assessment.

these findings were observed in a population with a high prevalence of oral anticoagulation at the time of brain MRI. Fourth, patients with an LNCCI had lower cognitive function than those without an LNCCI. The magnitude of this difference was similar for patients with silent infarcts, and similar to the effect of a previous stroke. Fifth, SNCI volume, white matter lesion volume, and microbleed count were not independently associated with cognitive function in a combined multivariable model including all lesion types. Finally, anticoagulation was not related to a higher microbleed count.

Comparing the prevalence of brain MRI lesions across studies is difficult because of differences in

FIGURE 2 MoCA Score Across Predefined Strata

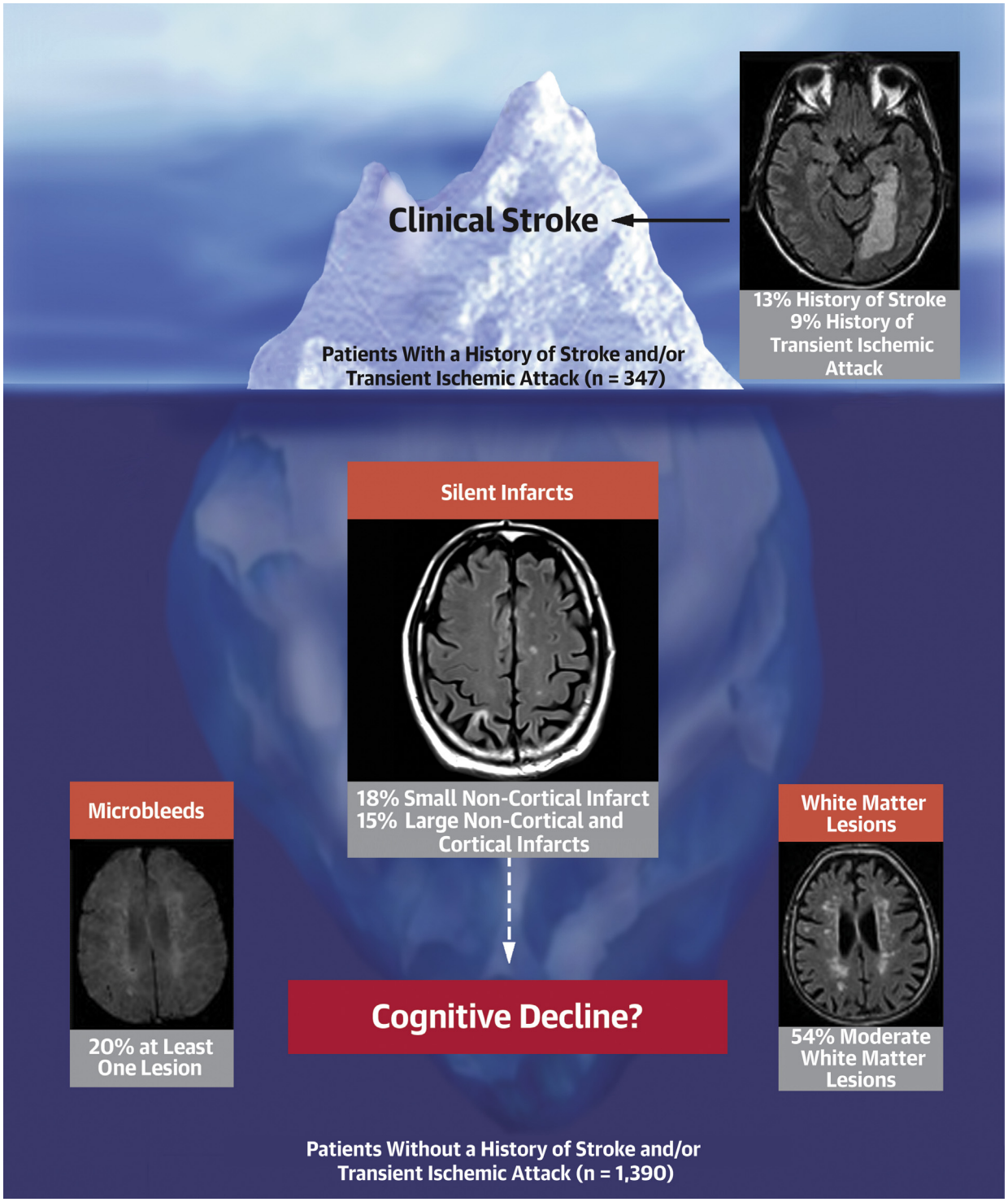


Data are mean ± SD; p values represent overall differences across strata and were obtained from linear mixed effects models with each strata variable as predictor and study center as random intercept. DOAC = direct oral anticoagulant; MoCA = Montreal Cognitive Assessment; VKA = vitamin K antagonist.

definitions and technologies. Nevertheless, the infarct prevalence of 37% in our study seems to be higher than in the general population, where the infarct prevalence was 31%. In addition, most of these infarcts were small (17). Another study found that the presence of clinically silent infarcts on brain MRI approximately doubled the risk of dementia and led to a steeper decline in cognitive function (18).

To understand the relationships between AF and cognitive impairment, we specifically assessed imaging markers of vascular disorders known to be associated with vascular dementia, which is the most common cause of dementia following Alzheimer's disease. Vascular dementia is a heterogeneous disorder caused by a variety of mechanisms (12), the most important of which are infarction of the brain cortex (multi-infarct dementia) and cerebral small vessel disease. When we corrected the impact of the different lesions types on cognition for each other, we found that only LNCCI was significantly associated with a significantly lower MoCA score. The magnitude of the difference was similar when only silent infarcts in patients without a history of stroke or TIA were considered. In contrast, none of the imaging markers of small vessel disease, including white matter lesions, SNCIs, and microbleeds, were associated with

CENTRAL ILLUSTRATION **Brain Lesions and Cognition in Patients With Atrial Fibrillation**



Conen, D. et al. J Am Coll Cardiol. 2019;73(9):989–99.

Potential relationships of overt and silent brain lesions with cognitive function in patients with atrial fibrillation.

cognitive impairment in the combined multivariable model. Therefore, silent LNCCIs but not small vessel disease may explain the association between AF and dementia in the absence of clinically overt strokes (**Central Illustration**) (5).

Although a 1-point MoCA score difference may seem small on an absolute scale, it is similar to a 10-year age difference or the presence of hypertension or diabetes (**Figure 2**). We therefore expect such a difference to be relevant from a clinical and societal perspective. Because the majority of brain infarcts were clinically silent and observed in patients without a history of stroke or TIA, our data raise the issue of brain MRI screening in patients with AF. Future studies should develop risk scores for AF patients that identify subgroups of AF patients who may benefit from brain imaging to better guide antithrombotic treatment in a cost-efficient manner. It is intriguing that permanent AF was associated with a lower MoCA score independent of covariates and brain lesion volumes (Online Table 3), a finding suggesting that the arrhythmia itself or associated treatments may have a direct effect on cognition. This supports findings from a prior study showing worse cognition in patients with AF but without evidence of brain infarcts on MRI (19).

Oral anticoagulation effectively prevents stroke in patients with AF (20). Although our cross-sectional analysis cannot address the question whether the cerebral infarcts occurred before or after initiation of oral anticoagulation, it nevertheless raises the issue that anticoagulation may not be sufficient to prevent a significant number of silent infarcts, especially those caused by mechanisms other than cardiac embolism. A combination of aspirin and low-dose rivaroxaban was significantly better than aspirin alone for stroke prevention among patients with stable vascular disease but without AF (21). Whether such a treatment strategy may also benefit patients with AF is currently unknown. Finally, both a history of hypertension and diabetes were significantly associated with lower MoCA scores in multivariable analyses, a finding suggesting that the high prevalence of cardiovascular risk factors in patients with AF may also contribute to the occurrence of overt and silent cerebral lesions.

Although its detailed histopathological correlates still need to be investigated, microbleeds are considered to be small hemorrhages in the brain (22). Patients with microbleeds have an increased risk of stroke and intracranial hemorrhage (23,24). In our study with a high prevalence of anticoagulation use, 22% of participants had microbleeds. This prevalence is similar to that in elderly individuals from the general population (25), or patients with ischemic stroke (26). Anticoagulation use was not associated with a higher microbleed count, and microbleed count was not associated with cognitive function. This finding is in agreement with data showing that aspirin and apixaban had a similar impact on the incidence of microbleeds (27). Currently available data therefore suggest that anticoagulation is safe in most patients with microbleeds, although it remains controversial whether there is a subgroup of patients with a high microbleed burden who should not be started on anticoagulation despite their high stroke risk (28,29).

STUDY STRENGTHS AND LIMITATIONS. Strengths of this study include the large sample size of well-characterized patients with AF, including the availability of brain MRI and cognitive testing. A potential limitation is the cross-sectional design of this analysis, precluding assessment of causality or directionality of effect. Participants in our study were mostly white, and all were enrolled in the compulsory Swiss health insurance system. Whether our data are applicable to other population groups or settings remains to be determined. Finally, our study included only patients with AF, and it is unclear how the prevalence of vascular brain lesions compares with that of other sample groups.

CONCLUSIONS

In this large study of well-treated patients with AF we found a high burden of vascular brain lesions on systematic brain MRI screening. Most of these lesions were previously unrecognized. Our analyses show that the presence of overt or silent LNCCIs on MRI have a similar impact on cognitive function as overt strokes, a finding suggesting that these lesions may explain at least part of the increased risk of cognitive dysfunction in these patients. Conversely, microbleeds were not significantly associated with cognitive function. Finally, the value of routine MRI scanning and cognitive function testing for better risk stratification of patients with AF should be assessed in further studies.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our study shows that most brain infarcts observed in patients with AF are clinically silent. Large numbers of silent and overt lesions were observed even though 90% of the patients were taking oral anticoagulant agents at the time of the brain MRI.

TRANSLATIONAL OUTLOOK: Future studies should evaluate whether and which patients with AF may benefit from brain MRI screening. These studies should also address the question of optimal antithrombotic treatment to prevent silent infarcts in patients with AF.

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KEY WORDS atrial fibrillation, cognitive dysfunction, microbleeds, silent cerebral infarcts, white matter lesions

APPENDIX For a complete list of Swiss-AF study investigators as well as supplemental tables, please see the online version of this paper.