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Atrial Fibrillation is Associated with Anterior Predominant White Matter Lesions in Patients Presenting with Embolic Stroke

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Abstract

Objective—High white matter hyperintensity (WMH) burden is commonly found on brain MRI among patients with atrial fibrillation (AF). However, whether the link between AF and WMH extends beyond a common vascular risk factor profile is uncertain. We sought to determine whether AF relates to a distinct WMH lesion pattern which may suggest specific underlying pathophysiological relationships.

Methods—We retrospectively analyzed a cohort of consecutive patients presenting with embolic stroke at an academic hospital and tertiary referral center between March 2010 and March 2014. 234 patients (53% female, 74% anterior circulation infarction) fulfilled the inclusion criteria and were included in the analyses. WMH lesion distribution was classified according to previously defined categories. Multivariable logistic regression analysis was performed to determine variables associated with AF within 90 days of index hospital discharge.

Results—Among included patients 114 had AF (49%). After adjustment for the CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke/TIA (doubled), vascular disease, age 65–74 years, sex category [female]) score, WMH

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Author contributions

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Competing Interests

Dr. Henninger serves on the advisory board of Omniox, Inc. All other authors declare no competing interests.

lesion burden as assessed on the Fazekas scale, embolic stroke pattern, infarct distribution, and pertinent interaction terms, AF was significantly associated with presence of anterior subcortical WMH patches (OR 3.647, 95% CI 1.681 to 7.911, $P=0.001$).

Conclusions—AF is associated with specific WMH lesion pattern among patients with embolic stroke etiology. This suggests that the link between AF and brain injury extends beyond thromboembolic complications to include a cardiovascularopathy that affects the brain and can be detected and characterized by WMH.

Keywords

atrial fibrillation; cardioembolism; cerebral infarction; leukoaraiosis; small vessel disease; topography; white matter

Introduction

White matter hyperintensity (WMH) lesions are commonly found on MRI and several studies found a high WMH lesion burden among patients with atrial fibrillation (AF).^{1–3} It has been hypothesized that AF mediates WMH pathogenesis through chronic silent microembolization.⁴ Indeed, conversion of acute small infarcts into WMH has been documented, which supports the notion that cerebral microembolism contributes the development of WMH.^{5,6} Though AF has been related to the severity of WMH, results regarding an independent association of AF with WMH have been conflicting.^{7–12}

A better understanding of the link between AF and WMH has the potential to provide insight into underlying pathophysiological mechanisms as well as open novel avenues to patient selection for costly diagnostic examinations or treatment decisions. For example, despite overall declining rates, cryptogenic stroke remains an important public health and clinical problem, accounting for 20–30% of all ischemic strokes.^{13,14} The majority of cryptogenic ischemic strokes are thought to be embolic in origin and AF is increasingly recognized as a cause.^{13,14} Diagnosing paroxysmal AF in this patient population remains a clinical challenge and only 5% of patients are diagnosed with AF at the time of their stroke.¹⁵ New guidelines suggest that more intensive monitoring leads to higher rates of AF detection, but cost and logistical challenges exist to long-term screening for AF among all patients with cryptogenic stroke.¹⁶ Defining novel imaging markers associated with AF might help better identify patients at risk for AF to better target these patients for further workup, including more intense AF screening.^{13,17} Although magnetic resonance imaging (MRI) is frequently used to assess infarct topography to provide clues regarding stroke etiology no infarct pattern has been identified that is pathognomonic for AF-related cerebral embolism.¹³ Likewise, no characteristic WMH pattern has been identified that links AF with WMH.

Using a previously established WMH lesion pattern system,¹⁸ we sought to determine whether WMH patterns differ between patients presenting with AF versus non-AF embolic ischemic stroke etiology, independent of the overall WMH lesion burden or vascular risk factor profile. Given the known association between AF and chronic brain microembolism^{5,6}

we hypothesized that AF preferentially relates to a WMH pattern characterized by multiple subcortical spots.¹⁸

Methods

Study cohort

We retrospectively analyzed 234 patients with acute ischemic stroke shown on brain MRI and included in the University of Massachusetts Memorial Medical Center Stroke registry between March 2010 and March 2014 followed for 90 days.^{19–21} In accord with our primary hypothesis, we included patients in whom the stroke etiology was defined as (i) definite or possible cardioembolic, (ii) non-cardioembolic but a cardioembolic cause could not be excluded (competing etiology), and (iii) patients with an embolic stroke of undetermined source. Given our stated goal to determine WMH patterns in patients with embolic stroke etiology, we excluded patients with large artery atherosclerosis and cerebral small vessel disease related stroke mechanism. We further restricted analyses to patients with brain MRI to reliably determine WMH and to exclude stroke mimics. Our investigation was approved by our Institutional Review Board (#H00006964) and Health Insurance Portability and Accountability Act waiver of informed consent granted. We adhere to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (www.strobe-statement.org).

Clinical characteristics, stroke etiology, and stroke severity

Patient demographics, laboratory data, co-morbidities, pre-admission medications were abstracted from the medical record by trained physician abstractors. Stroke etiology (using the Causative Classification System for ischemic stroke [CCS]²²) based on diagnostic evaluation, were collected on all patients (<http://ccs.mgh.harvard.edu>). In brief, the CCS is a free web-based, semi-automated, evidence-based classification system that assigns the most likely causative mechanism in a rule-based manner to 5 major categories (based on the Trial of ORG-10172 in Acute Stroke Treatment classification) patient with additional subdivision according to the weight of evidence (evident, probable, and possible) of an assignment.²² Members of the stroke team certified in NIHSS scoring graded the severity of stroke at presentation.

Risk factor definitions

We determined the presence of hypertension (use of antihypertensive medications, or systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg on 2 separate occasions), hypercholesterolemia (use of lipid-lowering agents, or fasting blood total cholesterol level of ≥ 200 mg/dl or low density lipoprotein cholesterol [LDLc] of ≥ 130 mg/dL) and diabetes mellitus (defined according to the National Diabetes Data Group and World Health Organization²³). Cardiac studies were obtained at the treating physicians' discretion and included transthoracic echocardiography or transesophageal echocardiography, electrocardiography, and 30-day event monitoring. All patients were submitted to continuous 24-hour in-patient cardiac telemetry per institutional protocol. For all participants, we calculated the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, prior stroke/TIA (doubled), vascular disease, age

65–74 years, sex category [female]) score (range 0 to 9) based on data available in the medical record. The qualifying stroke was counted towards the CHA₂DS₂-VASc-score; thus, the minimal possible score in our cohort was 2.

Atrial fibrillation

AF was defined according to the American Heart Association guidelines criteria.²⁴ Patients with AF in the setting of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair (valvular AF) were included in this study.^{24,25} For the purposes of our analyses, we considered AF present if AF was documented in the admission history, if AF was present on a per-protocol, admission 12-lead electrocardiogram, or if they had a history of oral anticoagulation for AF. In addition, abstractors reviewed all clinical notes, 30-day non-invasive monitor reports, implantable device reports (including pacemaker and implantable loop recorders), as well as all 12-lead ECGs obtained for any reason for newly diagnosed AF within 90 days of index hospital discharge.

Image analysis

WMH was defined on FLAIR MRI according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE)²⁶ criteria and graded according to the Fazekas scale as previously described in detail.^{19,27} The total Fazekas score was calculated by adding the periventricular and deep white matter lesion scores.¹⁹

WMH lesion patterns were defined by readers (Y.M., J.H.) who were blinded to clinical data and follow-up scans. Based on the grading scheme recently reported by Charidimou and colleagues (2016), we defined 5 WMH lesion patterns on FLAIR MRI (Figure 1).¹⁸ These patterns included: (i) multiple subcortical spots, (ii) large (extending more than 5 mm in the deep white matter) anterior subcortical patches (ASP), (iii) large posterior subcortical patches, and (iv) severe confluent subcortical WMH lesions. In addition, we denoted (v) an isolated periventricular pattern—this pattern was defined by the presence of WMH in contact with the ventricles in the absence of additional subcortical WMH lesions. Patients without WMH were included into this group. The previously reported peri-basal ganglia pattern (WMH following the peripheral outline of the basal ganglia) was present in 2 patients.¹⁸ These patients were coded according to their overlapping pattern: 1 with a severe confluent pattern and 1 with multiple subcortical spots. We tested the inter-observer reliability of the readers' assessment on 50 randomly chosen scans by Krippendorff's alpha test with 10,000 bootstrap samples.²⁸ This analysis demonstrated an excellent inter-observer agreement for WMH lesion pattern analysis ($\alpha=0.95$).

Statistics

Unless otherwise stated, continuous variables are reported as mean $\pm$ S.D. or median (25th–75th quartile). Categorical variables are reported as proportions. Between-group comparisons for continuous and ordinal variables were made with Mann-Whitney U test and Kruskal–Wallis one-way ANOVA by ranks as appropriate and correlations between the CHA₂DS₂-VASc score and Fazekas score were examined with Spearman rank correlation test. Categorical variables were compared using the χ^2 -test. Bonferroni method was used to correct for multiple comparisons.

To determine whether WMH lesion patterns (periventricular patches and ASP) were associated with AF (dependent variable) we constructed a multivariable logistic regression model adjusted for the CHA₂DS₂-VASc score and WMH lesion burden as assessed by the Fazekas score as well as the two-way and three-way interactions between WMH lesion pattern, Fazekas score, and CHA₂DS₂-VASc score. In addition, we adjusted for the presence of an embolic stroke pattern as well as presence of an anterior versus posterior circulation infarct distribution. Patients with both anterior and posterior circulation infarctions were categorized according to the vascular territory with the main infarct burden. To avoid model overfitting, a backward elimination method (likelihood ratio) was used for all models. Collinearity diagnostics were performed (and its presence rejected) for all multivariable regression models. The Hosmer-Lemeshow goodness-of-fit statistic was used to assess model fit.

Two-sided significance tests were used throughout and unless stated otherwise a two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM® SPSS® Statistics Version 22 (IBM®-Armonk, NY).

Results

Of 632 patients with ischemic stroke, 234 patients fulfilled the study criteria and were included. Of included patients, 114 had AF (49%) and 120 (51%) were not diagnosed with AF (Figure 2). A total of 156 (67%) patients had isolated anterior circulation strokes, 54 (23%) had isolated posterior circulation strokes, and 24 (10%) subjects had ischemic strokes both in the anterior and posterior circulation. Among patients with combined anterior and posterior circulation strokes the main infarct burden was in the anterior circulation in 18 and in the posterior circulation in 6 patients. Overall, 110 subjects had a definite cardioembolic stroke etiology (47%), 58 had a probable/possible cardioembolic stroke etiology (25%), 33 had a competing etiology (14%), and 33 had an embolic stroke of undetermined source (14%), respectively (Figure 2).

Baseline characteristics of included versus excluded patients with available MRI are summarized in Table 1. Overall, included patients were older, had a greater CHA₂DS₂-VASc-score, were more frequently female, and had a higher admission NIHSS ($P < 0.001$ each, Table 1). In addition, included patients more frequently had anterior circulation infarcts ($P = 0.038$), had a worse preadmission mRS ($P = 0.001$), more frequently had hypertension ($P = 0.017$) and were treated with antihypertensives ($P = 0.003$) as well as less frequently had diabetes mellitus ($P = 0.014$) and had a lower HbA1c ($P = 0.036$). Further, included patients had a lower LDLc ($P = 0.032$). There was no difference in the overall WMH lesion burden between included and excluded patients ($P = 0.190$) and cardiac workup was similar except for more frequent evaluation by transesophageal echocardiography of included patients ($P = 0.018$).

Baseline characteristics of included patients stratified by the AF-status are summarized in Table 2. Patients with AF were on average older ($P < 0.001$), more likely to be female ($P = 0.004$), more likely to be treated with an anticoagulant ($P < 0.001$) and antihypertensive medication ($P = 0.006$) on admission as compared with patients not diagnosed with AF. In

addition, patients with AF had higher admission NIHSS ($P<0.001$), baseline CHA₂DS₂-VASc score ($P<0.001$), and higher Fazekas score ($P=0.001$) as well as more frequently had ASP and less frequently had periventricular WMH patches as compared with patients without AF ($P<0.001$, each; Figure 3). Consistent with our focus on patients with embolic stroke etiology there was no difference in the prevalence of embolic appearing infarcts on MRI ($P=0.104$). Last, AF patients had a higher pre-stroke mRS ($P=0.021$). The prevalence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair was equally distributed between patients with AF ($n=9$; valvular AF) versus without AF ($n=11$; $P=0.817$). Although the overall WMH lesion pattern did not differ between these 20 patients ($P=0.322$, χ^2 -test), all patients ($n=2$) with an anterior subcortical WMH lesion pattern were in the valvular AF group.

Since AF and WMH share vascular risk factors included in the CHA₂DS₂-VASc score, we assessed associations between CHA₂DS₂-VASc score and WMH lesion burden, as well as between CHA₂DS₂-VASc score and WMH lesion patterns. As expected, we found a significant correlation between CHA₂DS₂-VASc score and Fazekas score ($\rho=0.470$, $P<0.001$; Figure 4). Further, the WMH lesion pattern distribution was significantly different between CHA₂DS₂-VASc score categories ($P<0.001$ for trend). On post-hoc analysis, subjects with a CHA₂DS₂-VASc score of 8 and 9 more frequently had ASP and a severe confluent pattern and less frequently had subcortical and large posterior patches as compared to patients with lower CHA₂DS₂-VASc scores ($P<0.05$, data not shown).

On multivariable logistic regression, presence of ASP ($P=0.001$) and higher CHA₂DS₂-VASc score ($P=0.002$) were significantly associated with AF (Table 3). The WMH severity, as assessed by the Fazekas score, presence of an embolic infarct pattern, and infarct location were not retained in the final model. Importantly, there was no interaction between ASP and the CHA₂DS₂-VASc as well as the Fazekas score showing that the association of ASP with AF was not dependent on the vascular risk factor and WMH lesion burden, respectively (Table 3).

Further, statistically significant associations between ASP and AF remained in sensitivity analyses that excluded patients with competing stroke etiologies ($n=201$; OR=4.516, 95% CI 1.932–10.556, $P=0.001$). Additionally, adjusting for treatment with antihypertensives, antidiabetics, antithrombotics, and baseline serum creatinine did not meaningfully change the results (data not shown). When we entered the individual vascular risk factors that are included in the CHA₂DS₂-VASc score instead of the summary score into the final step of the main multivariable model, presence of ASP ($P=0.005$), older age ($P<0.001$), presence of multiple infarcts ($P=0.024$), and presence of vascular disease ($P=0.020$) were independently associated with AF (data not shown). Lastly, because the original definition of the Fazekas scale distinguished between periventricular and deep WMH lesions, we conducted additional analyses to examine periventricular versus deep WMH lesion burden as both ordinal (each ranging from 0–3) or dichotomized (WMH present or absent) variables in lieu of the total Fazekas score. In univariable analyses, both greater periventricular ($P=0.005$) and deep ($P=0.001$) Fazekas scores were greater among AF patients (Table 2). Conversely, presence of periventricular ($P=0.002$) but not deep ($P=0.876$) WMH were associated with a non-AF stroke etiology (Table 2). After adjustment, the ASP lesion pattern remained

independently associated with AF ($P<0.01$ in all models) whereas periventricular and deep WMH (entered as dichotomized or ordinal variable) were not associated with AF (not shown).

Discussion

In this moderately sized cohort of patients with embolic stroke mechanism, MRI neuroimaging, and systematic assessment for AF, we observed that AF is associated with a distinct WMH lesion pattern. In contrast to our original hypothesis, we noted a statistically significant association between AF and anterior subcortical WMH patches. Relations between AF and this WMH pattern persisted even after rigorous adjustment for other potential covariates or confounders, including factors relating to an embolic stroke etiology and overall WMH lesion burden.

Given the typical locations of embolic infarcts in AF patients,²⁹ and the postulated link of AF to WMH through chronic silent microembolization^{4,5} we originally hypothesized that AF relates to a WMH pattern characterized by multiple subcortical spots. However, our contrasting finding of an independent association of ASP with AF challenges the view that chronic embolism accounts for AF-related WMH because preferential embolism into the anterior subcortical white matter is unlikely. Furthermore, our result of an absent association between WMH burden and AF after adjustment for vascular risk factors is in line with the majority of previous studies.^{7–12}

Our results may provide the impetus for further study to determine the specific pathomechanistical links between AF and WMH. Possibly, endothelial dysfunction or impaired cardiac output with chronic cerebral hypoperfusion might be contributing mechanisms.²¹ An alternative explanation may be an as of yet to be determined shared genomic link between AF and WMH. The possibility for such a link is supported by recent exciting observations: Genome-wide association studies have associated PITX2 with AF as well as stroke related to AF^{30,31} and subsequent investigations have linked PITX2 to cerebral small vessel disease related pathology providing a genetic rationale how AF may be uniquely linked to WMH.³²

The identification of a unique pathophysiological substrate for AF associated WMH may ultimately help us better understand clinical phenomena observed among patients with AF. For example, it is well established that AF patients are at elevated risk for poor post-stroke functional outcomes, cognitive impairment, and dementia, independent of incident strokes.^{21,33–36} The hypothesis that the association between small vessel disease related sequelae such as cognitive impairment is likely independent of established links between cardiovascular risk factors and overt ischemic stroke is further supported by observations that did not find a clear association between intracranial large artery and cerebral small vessel disease as well as absent association of intracranial large artery disease with cognitive impairment after adjustment for small vessel disease markers such as WMH.³⁷ Although the observational nature of our study precludes causal inference, our results do support the hypothesis that complex pathomechanisms that extend beyond clinically manifest thromboembolic events link AF to cognitive impairment and dementia because anterior

WMH topography has been associated with frontal cortical thinning and cognitive dysfunction.³⁸

Pending confirmation in future prospective studies, our findings may be of additional clinical relevance by using WMH pattern analysis as a readily assessable imaging biomarker that can help better target patients at high risk for AF for more intensive and cost-effective monitoring programs.³⁹ Nevertheless, our results should be considered cautiously and hypothesis generating only. Although we noted a high specificity (0.91) for the association of ASP with AF the sensitivity was low (0.30). Therefore, WMH pattern analysis should presently not be used as a clinical screening tool for AF.

Strengths of our study relate to inclusion of consecutive patients with MRI imaging, and evaluation of patterns by 2 blinded examiners, restriction of analyses to patients with suspected embolic infarct etiology, the rigorous adjustment for important factors associated with WMH, and protocol-driven, previously validated assessments for AF. Limitations relate to its retrospective and observational nature as well as moderate sample size. Thus, although we demonstrate a strong and novel association between AF and anterior subcortical WMH pattern, our research design does not allow us to infer causality. Not all patients without AF underwent long-term cardiac monitoring and analyses were restricted to the first 90-days after hospital discharge. Yet, while this may have caused us to underestimate the incidence of AF this would be expected to bias our results towards the null hypothesis. In addition, owing to the retrospective study nature we were unable to collect detailed information regarding the duration and type of AF. This, in conjunction with WMH quantification, may provide additional insight into the association between AF and WMH that will require elaboration in future, prospective studies.

Conclusion

Our study shows that AF is associated with anterior WMH lesion pattern on brain MRI. The clinical significance of this observation remains to be clarified, but our findings suggest that the established links between stroke and AF extend beyond thromboembolism and perhaps reflect an underlying cardiovascular pathology that can be characterized by WMH. Further investigation into the pathophysiological mechanisms underlying associations between WMH pattern and AF may provide novel avenues to enhance AF detection and stroke treatment.

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Figure 1.

White matter hyperintensity lesion patterns on fluid-attenuated inversion recovery MRI. (A) Isolated periventricular patches (PVP). (B) Multiple subcortical spots (SCS). (C) Large anterior subcortical patches (ASP). (D) Posterior subcortical patches (PSP). (E) Severe confluent subcortical patches (CSP). (F) White matter hyperintensity (WMH) lesion burden graded on the Fazekas scale and as stratified by the WMH patterns (Letters in bars denote the corresponding WMH lesion pattern; Kruskal-Wallis ANOVA on Ranks). Percent values indicate the relative prevalence of the observed WMH pattern in the investigated cohort.

Figure 2.
Case selection flow chart

Figure 3. Association of atrial fibrillation (AF) with white matter hyperintensity (WMH) lesion pattern. There was a significant association between the WMH lesion pattern and the AF-status ($P < 0.001$, χ^2 -Test).

Figure 4.

Correlation between the white matter hyperintensity (WMH) lesion burden as assessed by the Fazekas score and the CHA₂DS₂-VASc scores in the studied population ($\rho = 0.470$, $P < 0.001$). The degree of correlation was similar for patient with atrial fibrillation (AF; $\rho = 0.426$; $P < 0.001$) and without AF ($\rho = 0.456$; $P < 0.001$). Bubble size corresponds to the number of patients in each category (inset indicates the number of patients by bubble diameter; grey-scale is exclusively used to better differentiate circle size and is not proportional to the number of patients.).

Table 1

Baseline characteristics of the included versus excluded patients

Characteristics	Included patients (n=234)	Excluded patients (n=211)	P-value
Age, years	72 (62–85)	66 (58–73)	<0.001
CHA ₂ DS ₂ -VAsC-score	5 (4–6)	4 (3–6)	<0.001
Female sex	123 (53%)	74 (35%)	<0.001
Admission NIHSS	6 (2–12)	4 (2–9)	<0.001
Preadmission mRS	0 (0–1)	0 (0–1)	0.001
Laboratory data			
Admission glucose, mg/dL	121 (102–146)	121 (98–159)	0.836
Admission creatinine, mg/dL	0.97 (0.77–1.20)	0.96 (0.80–1.25)	0.619
HbA1c, %	6.0 (5.6–6.5)	6.1 (5.7–7.1)	0.036
LDLc, mg/dL	87 (68–112)	97 (73–125)	0.032
Cardiac evaluation			
Electrocardiogram	231 (99%)	205 (97%)	0.319
In-patient 24 hour cardiac telemetry	234 (100%)	211 (100%)	--
30-day event monitoring	85 (36%)	82 (39%)	0.624
Transthoracic echocardiogram	216 (92%)	191 (91%)	0.611
Transesophageal echocardiogram	21 (9%)	7 (3%)	0.018
Neuroimaging			
Anterior circulation infarction	174 (74%)	137 (65%)	0.038
Fazekas score	3 (2–4)	3 (2–4)	0.190
Preadmission medications			
Statin	106 (45%)	97 (46%)	0.924
Antihypertensive	172 (74%)	127 (60%)	0.003
Antiglycemic	50 (21%)	52 (25%)	0.431
Antiplatelets	113 (48%)	100 (47%)	0.924
Oral anticoagulant	26 (11%)	14 (7%)	0.134
Preexisting risk factors			
Hypertension	192 (82%)	153 (73%)	0.017
Hyperlipidemia	132 (56%)	123 (58%)	0.702
Diabetes	62 (27%)	79 (37%)	0.014
Prior stroke or TIA	43 (18%)	42 (20%)	0.718
Congestive heart failure	27 (12%)	15 (7%)	0.143
Peripheral artery disease	64 (27%)	49 (23%)	0.328

CHA₂DS₂-VAsC indicates congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, previous stroke/TIA (doubled), vascular disease, age 65–74 years, sex category (female); HbA1c, glycated hemoglobin A1c; LDLc, low-density lipoprotein; cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensity. Data are n (%) or median (25th–75th quartiles).

Table 2

Baseline characteristics (unadjusted) of the studied patient population as stratified by AF vs non-AF embolic stroke etiology.

Characteristics	AF present (n=114)	AF absent (n=120)	P-value
Age, years	79 (69–85)	64 (55–79)	<0.001
CHA ₂ DS ₂ -VASc-score	6 (5–6)	5 (4–6)	<0.001
Female sex	71 (63%)	52 (43%)	0.004
Admission NIHSS	8 (4–16)	4 (2–9)	<0.001
Preadmission mRS	0 (0–1)	0 (0–1)	0.021
Laboratory data			
Admission glucose, mg/dL	121 (103–140)	120 (101–154)	0.906
Admission creatinine, mg/dL	0.93 (0.78–1.15)	1.00 (0.76–1.22)	0.342
HbA1c, % (n=216)	6.0 (5.7–6.5)	5.9 (5.6–6.6)	0.920
LDLc, mg/dL (n=220)	84 (68–101)	91 (67–123)	0.073
Cardiac evaluation			
Electrocardiogram	112 (98%)	119 (99%)	0.614
In-patient 24 hour cardiac telemetry	114 (100%)	120 (100%)	--
30-day event monitoring	14 (12%)	71 (59%)	<0.001
Transthoracic echocardiogram	99 (87%)	117 (98%)	0.003
Transesophageal echocardiogram	3 (3%)	18 (15%)	0.001
Neuroimaging			
Anterior circulation infarction	91 (80%)	83 (69%)	0.062
Multiple acute infarcts	36 (32%)	51 (43%)	0.104
Total Fazekas score	3 (2–4)	2 (2–4)	0.001
Periventricular Fazekas score	2 (1–2)	1 (1–2)	0.005
Deep Fazekas score	1 (1–2)	1 (1–2)	0.001
Presence of any periventricular WMH	34 (30%)	60 (50%)	0.002
Presence of any deep WMH	26 (23%)	26 (22%)	0.876
WMH lesion pattern			
Periventricular	34 (30%)	60 (50%)	0.002
Subcortical spots	26 (23%)	26 (22%)	0.834
Anterior subcortical patches	34 (30%)	11 (9%)	<0.001
Posterior subcortical patches	18 (16%)	16 (13%)	0.594
Severe confluent subcortical patches	2 (2%)	7 (6%)	0.105
Preadmission medications			
Statin	51 (45%)	55 (46%)	0.866
Antihypertensive	93 (82%)	79 (66%)	0.006
Antiglycemic	23 (20%)	27 (23%)	0.665
Antiplatelets	58 (51%)	55 (46%)	0.440
Oral anticoagulant	22 (19%)	4 (3%)	<0.001
Preexisting risk factors			
Hypertension	100 (88%)	92 (77%)	0.028

Characteristics	AF present (n=114)	AF absent (n=120)	P-value
Hyperlipidemia	60 (53%)	72 (60%)	0.256
Diabetes	26 (23%)	36 (30%)	0.213
Prior stroke or TIA	25 (22%)	18 (15%)	0.171
Congestive heart failure	12 (11%)	15 (13%)	0.654
Peripheral artery disease	27 (24%)	37 (31%)	0.220

AF indicates atrial fibrillation; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, previous stroke/TIA (doubled), vascular disease, age 65–74 years, sex category (female); HbA_{1c}, glycated hemoglobin A_{1c}; LDLc, low-density lipoprotein; cholesterol; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; WMH, white matter hyperintensity. Data are n (%) or median (25th–75th quartiles).

Table 3

Multivariable logistic regression analysis with backward elimination of factors independently associated with atrial fibrillation

Independent variable	crude OR (95% CI)	P-value	adjusted OR (95% CI)	P-value
ASP	4.211 (2.011 to 8.814)	<0.001	3.647 (1.681 to 7.911)	0.001
PVP	0.425 (0.248 to 0.728)	0.002	--	--
CHA ₂ DS ₂ -VASc	1.384 (1.165 to 1.644)	<0.001	1.329 (1.110 to 1.591)	0.002
Fazekas score	1.328 (1.123 to 1.570)	0.001	--	--
ASP × Fazekas	1.357 (1.138 to 1.619)	0.001	--	--
PVP × Fazekas	0.872 (0.684 to 1.112)	0.270	--	--
ASP × CHA ₂ DS ₂ -VASc	1.262 (1.115 to 1.429)	<0.001	--	--
PVP × CHA ₂ DS ₂ -VASc	0.901 (0.805 to 1.009)	0.070	--	--
CHA ₂ DS ₂ -VASc × Fazekas	1.051 (1.025 to 1.078)	<0.001	--	--
ASP × CHA ₂ DS ₂ -VASc × Fazekas	1.053 (1.022 to 1.085)	0.001	--	--
PVP × CHA ₂ DS ₂ -VASc × Fazekas	0.994 (0.951 to 1.039)	0.796	--	--
Posterior circulation infarction	0.567 (0.311 to 1.033)	0.064	0.558 (0.290 to 1.072)	0.080
Multiple acute infarcts	0.624 (0.365 to 1.067)	0.085	0.585 (0.327 to 1.045)	0.070

Dashes indicate that the variable was not retained in the final step of the multivariable model; ASP, large anterior subcortical patches; PVP, periventricular pattern; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, previous stroke/TIA (doubled), vascular disease, age 65–74 years, sex category (female).