Leukoaraiosis and stroke recurrence risk in patients with and without atrial fibrillation

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ABSTRACT

Objective: We aimed to investigate the association between leukoaraiosis and long-term risk of stroke recurrence adjusting for clinical scores developed and validated for the prediction of stroke risk, such as $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or TIA) and CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category).

Methods: Study population was derived from the Athens Stroke Registry and was categorized in 2 subgroups according to the presence of atrial fibrillation (AF). Cox proportional hazards analysis was performed to assess the independent predictors of stroke recurrence. To investigate whether leukoaraiosis adds to the prognostic accuracy of $CHADS_2$ and CHA_2DS_2-VASc scores, we used the likelihood ratio test. Overall model assessment was performed with Nagelkerke R^2 and Harrell C statistic. Kaplan–Meier analyses were also performed.

Results: Among 1,892 patients, there were 320 (16.9%) with leukoaraiosis and 670 (35.4%) with AF. In the Kaplan–Meier analysis, there was significant difference in cumulative probability of stroke recurrence between patients with and without leukoaraiosis in the non-AF group ($p < 0.01$), but not in the AF group ($p = 0.46$). On Cox multivariate analysis, leukoaraiosis was found to be a significant independent predictor of stroke recurrence only in the non-AF group, in the models adjusting for $CHADS_2$ (hazard ratio: 1.86, 95% confidence interval: 1.35–2.56) and CHA_2DS_2-VASc (hazard ratio: 1.82, 95% confidence interval: 1.32–2.51) scores. Leukoaraiosis was not a predictor of stroke recurrence in the AF group. Leukoaraiosis did not improve the predictive accuracy of the 2 scores, whether in the non-AF group (Harrell C statistic: 0.56 vs 0.59 [$p = 0.31$] for the model including $CHADS_2$; 0.56 vs 0.59 [$p = 0.44$] for the model including CHA_2DS_2-VASc) or the AF group (Harrell C statistic: 0.63 vs 0.62 for the model including $CHADS_2$; 0.64 vs 0.64 for the model including CHA_2DS_2-VASc).

Conclusions: Leukoaraiosis is an independent predictor of stroke recurrence in non-AF stroke patients. However, leukoaraiosis did not increase the accuracy of the $CHADS_2$ and CHA_2DS_2-VASc scores to predict stroke recurrence in AF or non-AF stroke patients. ***Neurology*® 2015;84:1–7**

GLOSSARY

AF = atrial fibrillation; **$CHADS_2$** = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or TIA; **CHA_2DS_2-VASc** = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category; **CI** = confidence interval; **HR** = hazard ratio; **NIHSS** = NIH Stroke Scale.

There is controversy whether leukoaraiosis can be helpful for the estimation of the risk of stroke recurrence. One recent study showed that the extent of leukoaraiosis is an independent predictor of 90-day stroke recurrence.[1] Similar results were also reported from older studies.[2–5] However, none of these studies adjusted for externally well-validated clinical risk scores that were developed and validated for the prediction of stroke risk, such as the $CHADS_2$ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or TIA) or CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category). Indeed, these 2 scores are reliable predictors of stroke

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recurrence in patients with[6–8] and without atrial fibrillation (AF)[9] and are used widely in clinical practice to aid in the estimation of stroke risk. On the contrary, other studies failed to identify an association between leukoaraiosis and stroke recurrence.[10–12]

In the present study, we aimed to analyze a large series of consecutive stroke patients from a prospective stroke registry to investigate the association between leukoaraiosis and long-term risk of stroke recurrence, adjusting for $CHADS_2$ and CHA_2DS_2-VASc scores. We tested the hypothesis that leukoaraiosis would be correlated to $CHADS_2$ and CHA_2DS_2-VASc scores, and second, leukoaraiosis would add to the prognostic accuracy of both scores.

METHODS

Study population and definitions. The study population was derived from the Athens Stroke Registry, which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece, between June 1992 and August 2012.[13] Patients with TIA or recurrent stroke are not included in the registry.

Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, stroke mechanism, clinical-laboratory findings and vital signs at admission, laboratory investigations, and medication at discharge. Stroke severity was assessed by means of the NIH Stroke Scale (NIHSS) score at admission.[14] The $CHADS_2$ score was calculated with the following parameters: congestive heart failure, hypertension, age 75 years or older, diabetes mellitus (1 point each), and prior stroke or TIA (2 points).[6,7] The CHA_2DS_2-VASc score was calculated with the following parameters: congestive heart failure, hypertension, age (1 point if 65–74 years; 2 points if 75 years or older), diabetes mellitus, previous stroke/TIA (2 points), vascular disease, and sex category (1 point if female).[8] For the present analysis, the prestroke $CHADS_2$ and CHA_2DS_2-VASc scores were considered.

Leukoaraiosis was defined as patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted MRI in periventricular or subcortical regions, or in the pons,[15] and was diagnosed by board-certified consultant radiologists. Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg diagnosed at least twice before stroke or if patient was already on antihypertensives.[16] Diabetes mellitus was defined as fasting blood glucose level >6.0 mmol/L before stroke or if patient was already on antidiabetic drugs and/or insulin.[17] Dyslipidemia was defined as cholesterol concentration >6.5 mmol/L the day after admission or if patient had a previous diagnosis of dyslipidemia.[18] Coronary heart disease was assessed by questionnaire and relevant medical confirmation. Heart failure was defined according to the criteria recommended by the working group on heart failure of the European Society of Cardiology.[19] TIA was defined as complete disappearance of signs and symptoms within 24 hours, regardless of infarction being shown on neuroimaging.[20] Stroke was defined according to the World Health Organization criteria.[21]

A 12-lead ECG was recorded at admission in all patients. All patients were evaluated by the study cardiologist, and AF was documented by means of repeated ECGs during hospital stay, and/or continuous ECG monitoring for several days for patients treated in the stroke unit, and/or 24-hour Holter ECG monitoring (when AF was strongly suspected from the clinical presentation and brain imaging findings).

Patients were followed up prospectively at the outpatient clinic at 1, 3, and 6 months after hospital discharge and yearly thereafter for up to 10 years or until death. For those patients who were unable to attend the outpatient clinic, follow-up was assessed by telephone interview with the patient or proxies, or at the patient's residence.

Statistical analysis. Continuous data are summarized as median value and interquartile range, and categorical data as absolute number and percentage. Dichotomous or categorical variables were compared with the χ^2 test (or Fisher exact test whenever χ^2 test assumptions were violated) and continuous variables were compared with the Wilcoxon rank sum test. Statistical analyses were performed with the Statistical Package R (version 3.1.1).

The Kaplan–Meier product limit method was used to estimate the cumulative probability of stroke recurrence between patients with and without leukoaraiosis in the AF and non-AF subgroups during follow-up. Differences in Kaplan–Meier curves among patient groups were evaluated with the log-rank test.

Cox proportional hazards analysis was performed to assess the independent predictors of stroke recurrence. The covariates included in the analysis were age, sex, stroke severity assessed by the NIHSS score, stroke subtype by TOAST (Trial of Org 10172 in Acute Stroke Treatment) mechanism, cardiovascular risk factors and comorbidities (history of hypertension, diabetes, dyslipidemia, heart failure, ischemic heart diseases, peripheral vascular diseases, previous thromboembolism, previous TIA), the prestroke $CHADS_2$ and CHA_2DS_2-VASc scores, prestroke medication (antiplatelets), systolic and diastolic pressure at admission, leukoaraiosis diagnosed, treatment during hospitalization (thrombolysis, aspirin, anticoagulants), and recommended treatment at discharge (antiplatelets, warfarin).

To investigate whether leukoaraiosis adds in the prognostic accuracy of the $CHADS_2$ and CHA_2DS_2-VASc scores, we used 2 methodologic approaches: the first one was Nagelkerke R^2, providing an estimate of the total variability explained by our model (a similar measure of the R^2 statistic in the classic regression analysis). The second statistical analysis that was used to investigate whether leukoaraiosis adds in the prognostic accuracy of the $CHADS_2$ or the CHA_2DS_2-VASc scores was the Harrell C statistic, a rank correlation measure for censored survival data.[22]

To investigate whether there was any interaction between the imaging modality used to assess leukoaraiosis (CT or MRI), the time period that the patient was admitted (early years vs later years), and the results of the analysis, we performed 2 sensitivity analyses: in the first, we included only MRI-scanned patients; in the second, we included only patients admitted after 2002.

Associations are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The level of statistical significance was set at 5%. Patients with complete data in the response and the covariates were included in the analysis.

Standard protocol approvals, registrations, and patient consents. The scientific use of the data collected in the Athens Stroke Registry was approved by the local ethics committee.

RESULTS

Between 1992 and 2011, 2,870 patients were included in the Athens Stroke Registry. Of them, 1,892 patients (65.9%) (1,169 [61.8%] females, median age: 71.0 ± 15.0 years) with acute first-ever ischemic

stroke had available information about leukoaraiosis. Of them, 617 patients (32.6%) were investigated with brain MRI, and 1,275 (67.4%) with brain CT. Leukoaraiosis was detected in 320 (16.9%) of them, and 670 (35.4%) had AF. The baseline characteristics of patients regarding AF and leukoaraiosis status are summarized in the table. Among the overall population of 1,892 patients, 351 (18.6%) had a recurrent stroke during a median follow-up of 30.0 months (interquartile range: 5.0–79.0).

AF subgroup. There were 22 (19.0%) stroke recurrences in patients with leukoaraiosis and 106 (19.1%) in patients without leukoaraiosis. On Kaplan–Meier analysis, there was no significant difference in the cumulative probability of stroke recurrence between patients with and without leukoaraiosis (log-rank test: 0.50, $p = 0.46$) (figure 1A).

The Cox model analysis including also the $CHADS_2$ score showed that leukoaraiosis was not an independent predictor of stroke recurrence (HR: 1.02, 95% CI: 0.63–1.66, $p = 0.92$) in contrast to the independent prediction of the $CHADS_2$ score (HR: 1.22, 95% CI: 1.05–1.41, $p = 0.01$), NIHSS score (HR: 0.97, 95% CI: 0.94–0.99, $p = 0.01$), and anticoagulation treatment at discharge ($p = 0.02$). The 2 models with and without leukoaraiosis had comparable Nagelkerke R^2 (0.043), while they differed slightly in the Harrell C statistic (0.63 vs 0.62).

Similarly, in the Cox model analysis including the CHA_2DS_2-VASc score, leukoaraiosis was not an independent predictor of stroke recurrence (HR: 0.99, 95% CI: 0.61–1.60, $p = 0.96$) in contrast to the independent prediction of the CHA_2DS_2-VASc score (HR: 1.22, 95% CI: 1.07–1.38, $p < 0.01$), NIHSS score (HR: 0.96, 95% CI: 0.94–0.99, $p < 0.01$), and anticoagulant treatment at discharge ($p = 0.03$). Nagelkerke R^2 and Harrell C statistic for the models with and without leukoaraiosis along with the CHA_2DS_2-VASc score were similar (0.048 and 0.64, respectively).

The annual stroke recurrence rate in the AF subgroup stratified by the $CHADS_2$ and CHA_2DS_2-VASc scores, and leukoaraiosis is presented in figure 2A.

Non-AF subgroup. There were 49 (24.0%) stroke recurrences in patients with leukoaraiosis and 174 (17.1%) in patients without leukoaraiosis. In the Kaplan–Meier analysis, there was significant difference in the cumulative probability of stroke recurrence between patients with and without leukoaraiosis (log-rank test: 13.4, $p < 0.01$) (figure 1B).

The Cox model analysis including also the $CHADS_2$ score showed that leukoaraiosis (HR: 1.86, 95% CI: 1.35–2.56, $p < 0.01$) and the $CHADS_2$ score (HR: 1.21, 95% CI: 1.08–1.36, $p < 0.01$) were the only independent predictors of stroke recurrence. Although the Nagelkerke R^2 of the model with the $CHADS_2$ score (0.010) was numerically lower than the corresponding R^2 of the model combining the $CHADS_2$ and leukoaraiosis (0.021), this difference was not statistically significant ($p = 0.46$). Similarly, using Harrell C statistic, adding leukoaraiosis to the $CHADS_2$ score did not improve its predictive accuracy for recurrent stroke (0.56 vs 0.59, $p = 0.31$).

Similarly, in the Cox model analysis including the CHA_2DS_2-VASc score, leukoaraiosis (HR: 1.82, 95% CI: 1.32–2.51, $p < 0.01$) and the CHA_2DS_2-VASc score (HR: 1.15, 95% CI: 1.05–1.25, $p < 0.01$) were the only independent predictors of stroke recurrence. Although the Nagelkerke R^2 of the CHA_2DS_2-VASc score (0.011) was numerically smaller than the corresponding figure of the model combining the CHA_2DS_2-VASc and leukoaraiosis (0.021), this difference was not statistically significant ($p = 0.48$). Similarly, using Harrell C statistic, adding leukoaraiosis to the CHA_2DS_2-VASc score did not improve its predictive accuracy for recurrent stroke (0.56 vs 0.59, $p = 0.44$).

The annual stroke recurrence rate in the non-AF subgroup stratified by the $CHADS_2$ and CHA_2DS_2-VASc scores, and leukoaraiosis is presented in figure 2B.

Sensitivity analyses. In a sensitivity analysis including only MRI-scanned patients, leukoaraiosis was significantly associated with stroke recurrence in the non-AF subgroup (HR: 2.18, 95% CI: 1.34–3.54 in the model including the $CHADS_2$ score, and HR: 2.23, 95% CI: 1.37–3.62 in the model including the CHA_2DS_2-VASc score). There was no association between leukoaraiosis and stroke recurrence in the AF subgroup (HR: 1.82, 95% CI: 0.54–6.16 in the model including the $CHADS_2$ score, and HR: 1.83, 95% CI: 0.55–6.17 in the model including the CHA_2DS_2-VASc score).

In a sensitivity analysis including only patients recruited after 2002, leukoaraiosis was significantly associated with stroke recurrence in the non-AF subgroup (HR: 2.78, 95% CI: 1.61–4.79 in the model including the $CHADS_2$ score, and HR: 2.78, 95% CI: 1.61–4.78 in the model including the CHA_2DS_2-VASc score). There was no association between leukoaraiosis and stroke recurrence in the AF subgroup (HR: 1.13, 95% CI: 0.25–5.04 in the model including the $CHADS_2$ score, and HR: 1.06, 95% CI: 0.24–4.79 in the model including the CHA_2DS_2-VASc score).

DISCUSSION The present study analyzed a large series of consecutive stroke patients to investigate the role of leukoaraiosis in the prediction of stroke recurrence. We show that leukoaraiosis was an independent predictor of stroke recurrence in patients without AF, but not in patients with AF. Leukoaraiosis did not

increase the predictive accuracy for recurrent stroke of the $CHADS_2$ and CHA_2DS_2-VASc scores, whether in patients with or without AF.

A few studies have previously investigated the prognostic role of leukoaraiosis for the prediction of stroke recurrence: recently, the extent of leukoaraiosis (graded as mild [<2] and extensive [≥2] on fluid-attenuated inversion recovery images obtained within 72 hours after stroke onset in the hemisphere contralateral to acute stroke) was shown to be an independent predictor of 90-day stroke recurrence.[1] Similar results were also obtained from older studies.[2–5]

Table Patient characteristics stratified by AF and leukoaraiosis

	AF (n = 670)			Non-AF (n = 1,222)		
	Leukoaraiosis (n = 116)	No leukoaraiosis (n = 554)	*p* Value	Leukoaraiosis (n = 204)	No leukoaraiosis (n = 1,018)	*p* Value
Demographics						
Sex, female	52 (44.8)	276 (49.8)	0.38	141 (69.1)	700 (68.8)	0.09
Age, y	80.0 (74.8–83.3)	75.0 (69.0–81.0)	<0.01	72.0 (66.0–80.0)	68.0 (58.0–74.0)	0.01
Stroke mechanism (TOAST)						
Lacunar	4 (3.4)	18 (3.2)	0.34	102 (50.0)	305 (30.0)	0.01
Large artery atherosclerotic	3 (2.9)	16 (2.9)		34 (16.7)	300 (29.5)	
Cardioembolic	97 (83.6)	488 (88.1)		15 (7.4)	107 (10.5)	
Cryptogenic	12 (10.3)	32 (5.8)		51 (25.0)	263 (25.8)	
Other determined cause	NA	NA		2 (1.0)	43 (4.2)	
Comorbidities/risk factors						
Hypertension	84 (72.4)	397 (71.7)	0.96	174 (85.3)	740 (72.7)	0.01
Diabetes mellitus	27 (23.3)	123 (22.2)	0.89	51 (25.0)	319 (31.3)	0.08
Smoking	28 (24.1)	101 (18.2)	0.18	76 (37.3)	388 (38.1)	0.87
Previous TIA	10 (8.6)	39 (7.0)	0.69	30 (14.7)	158 (15.5)	0.85
Heart failure	17 (14.7)	78 (14.1)	0.98	13 (6.4)	78 (7.7)	0.62
Dyslipidemia	40 (34.5)	161 (29.1)	0.29	93 (45.6)	508 (49.9)	0.29
Coronary artery disease	24 (20.7)	111 (20.0)	0.97	50 (24.5)	238 (23.4)	0.77
Prestroke $CHADS_2$ score						
Continuous	2.0 (1.0–3.0)	2.0 (1.0–2.0)	0.01	2.0 (1.0–3.0)	2.0 (1.0–2.0)	0.01
0	9 (7.8)	70 (12.6)	0.01	11 (5.4)	158 (15.6)	0.01
1	25 (21.6)	172 (31.0)		73 (35.8)	343 (33.9)	
2	38 (32.8)	191 (34.5)		64 (31.4)	304 (30.0)	
>2	44 (37.9)	121 (21.8)		56 (27.5)	207 (20.5)	
Prestroke CHA_2DS_2-VASc score						
Continuous	4.0 (3.0–5.0)	3.0 (2.0–4.0)	0.01	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.01
0	0 (0.0)	8 (1.4)	0.02	2 (1.0)	68 (6.7)	0.01
1	5 (4.3)	40 (7.2)		17 (8.3)	149 (14.7)	
2	10 (8.6)	96 (17.3)		46 (22.5)	208 (20.6)	
>2	101 (87.1)	410 (74.0)		139 (68.1)	587 (58.0)	
Clinical and laboratory measures						
Systolic blood pressure, mm Hg	150.0 (130.0–170.0)	150.0 (140.0–170.0)	0.32	160.0 (140.0–180.0)	150.0 (140.0–170.0)	0.01
Diastolic blood pressure, mm Hg	80.0 (80.0–90.0)	85.0 (80.0–90.0)	0.76	90.0 (80.0–100.0)	86.0 (80.0–90.0)	0.01
NIHSS score	12.0 (3.8–20.0)	12.0 (3.0–21.0)	0.57	4.0 (2.0–9.0)	4.0 (2.0–11.0)	0.18
Treatment during hospitalization						
Aspirin	80 (69.0)	424 (76.5)	0.11	160 (78.4)	852 (83.7)	0.08
Thrombolysis	9 (7.8)	14 (2.5)	0.01	0 (0.0)	15 (1.5)	0.15
Anticoagulants	52 (44.8)	331 (59.7)	0.01	82 (40.2)	518 (50.9)	0.01

Continued

Table Continued

	AF (n = 670)			Non-AF (n = 1,222)		
	Leukoaraiosis (n = 116)	No leukoaraiosis (n = 554)	*p* Value	Leukoaraiosis (n = 204)	No leukoaraiosis (n = 1,018)	*p* Value
Anticoagulants at discharge						
None	17 (18.3)	58 (13.4)	0.07	18 (9.4)	44 (4.7)	0.01
Antiplatelets only	48 (51.6)	190 (43.9)		169 (88.0)	829 (88.0)	
Warfarin only	28 (30.1)	185 (42.7)		5 (2.6)	69 (7.3)	
Antiplatelet plus warfarin	4 (3.4)	28 (5)		2 (1.0)	15 (1.5)	

Abbreviations: AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or TIA; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category; NA = not applicable; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.
Continuous variables are presented as median (interquartile range). Nominal variables are presented as absolute number (percent) (percent refers to recorded values only; missing values have been excluded).

However, these studies did not adjust for the $CHADS_2$ or CHA_2DS_2-VASc risk scores in these studies; given that these scores were shown to reliably predict stroke recurrence both in patients with AF[6–8] and those without AF,[9] inclusion of these scores in the models along with leukoaraiosis might have diluted its prognostic effect. Recently, leukoaraiosis was shown to have a significant prognostic role in stroke outcome in young patients.[12] On the contrary, other studies failed to identify an independent association between leukoaraiosis and stroke outcome, adding further to the controversy of whether leukoaraiosis is an independent predictor of stroke recurrence.[10,11]

The exact mechanism underlying the discrepancy in the prognostic role of leukoaraiosis between patients with and without AF is unclear. The most putative explanation is that in patients with AF, the association between anticoagulant treatment and stroke recurrence is too powerful to permit the detection of a (much weaker) association between leukoaraiosis and stroke recurrence. However, in patients without AF, there is a significant association between leukoaraiosis and stroke recurrence, even after adjusting for chronic conditions that predispose to leukoaraiosis such as hypertension and diabetes mellitus.

The present study is limited by its single-center character, which may have introduced selection bias compared with a population-wide setting. Also, this is a retrospective analysis of prospectively collected data, which may have introduced collection and registration bias, and possibly residual confounding, as implied by the large proportion of female patients and the large number of patients excluded from the study because of missing leukoaraiosis data. Moreover, other potential confounders were not assessed, such as adherence to secondary prevention measures, e.g., antiplatelets, antihypertensives, and statins. Also,

Figure 1 Cumulative probability of being free of stroke recurrence in patients with atrial fibrillation (A) and patients without atrial fibrillation (B) stratified by leukoaraiosis

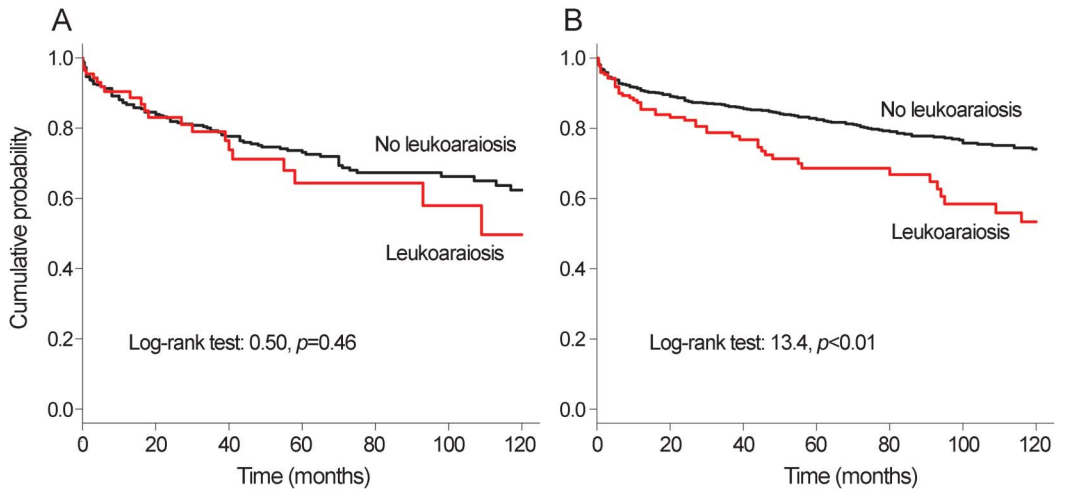
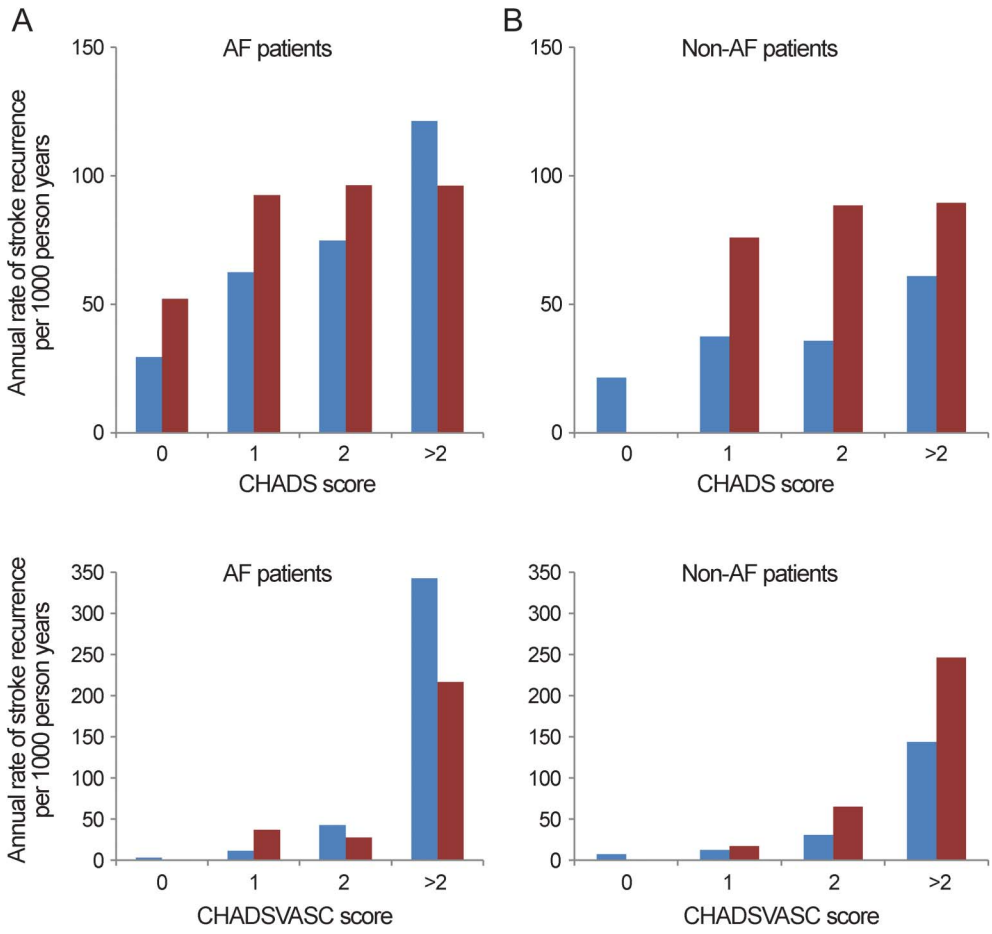


Figure 2 Annual stroke recurrence rate stratified by $CHADS_2$ and CHA_2DS_2-VASc scores, leukoaraiosis, and AF



(A) Patients with AF. (B) Patients without AF. Red = leukoaraiosis; blue = no leukoaraiosis. AF = atrial fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and stroke or TIA; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years, sex category.

only one-third of patients underwent MRI for the diagnosis of leukoaraiosis, which may be more sensitive than CT, the scanning method used in the majority of patients. This may have introduced bias given that the 2 methods have different accuracy to identify leukoaraiosis; however, the sensitivity analysis on the MRI-scanned subpopulation yielded similar results with the overall population. Also, we did not use a standardized method to grade leukoaraiosis, e.g., the Fazekas scale, which may have improved its prognostic accuracy. In contrast, strengths of the study include the prospective nature of this registry, the large number of consecutive patients registered within a wide time window of 20 years, the large number of outcome events, and the long follow-up.

Leukoaraiosis is an independent predictor of stroke recurrence in patients without AF, but not in patients with AF. However, leukoaraiosis did not increase the accuracy of the $CHADS_2$ and CHA_2DS_2-VASc scores to predict stroke recurrence in AF or non-AF stroke patients.

AUTHOR CONTRIBUTIONS

G. Ntaios: study concept, statistical analysis and interpretation, preparation of manuscript, study supervision. G.Y.H. Lip: study concept, interpretation of results, critical revision of the manuscript. D. Lambrou: statistical analysis and interpretation, critical revision of the manuscript. V. Papavasileiou: critical revision of the manuscript. E. Manios: critical revision of the manuscript. H. Milionis: critical revision of the manuscript. K. Spengos: critical revision of the manuscript. K. Makaritsis: critical revision of the manuscript. K. Vemmos: acquisition of data, study concept, statistical analysis and interpretation, critical revision of manuscript.

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