CHADS2, CHA2DS2-VASc, and long-term stroke outcome in patients without atrial fibrillation


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ABSTRACT

Objective: CHADS₂ and CHA₂DS₂-VASc scores are used to assess stroke risk in patients with atrial fibrillation (AF). We investigated whether these scores are associated with stroke outcome in non-AF stroke patients.

Methods: Consecutive patients with acute first-ever ischemic stroke but without AF were classified into subgroups according to prestroke CHADS₂ and CHA₂DS₂-VASc scores and followed up for 5 years. The end points were death, stroke recurrence, and a composite of major cardiovascular events.

Results: Among 1,756 patients (aged 67.2 ± 12.3 years, 68.2% males), there were 258 (14.7%), 617 (35.3%), and 878 (50.0%) patients with low, intermediate, and high CHADS₂ score, respectively. The corresponding figures for CHA₂DS₂-VASc subgroups were 110 (6.3%), 255 (14.5%), and 1,391 (79.2%). There were significant differences between CHADS₂ subgroups in 5-year mortality (log-rank test = 74.5, \( p < 0.0001 \)), stroke recurrence (log-rank test = 12.3, \( p = 0.002 \)), and cardiovascular events (log-rank test = 19.4, \( p < 0.001 \)). Similarly, there were significant differences between CHA₂DS₂-VASc subgroups in 5-year mortality (log-rank test = 74.5, \( p < 0.0001 \)), stroke recurrence (log-rank test = 10.6, \( p = 0.005 \)), and cardiovascular events (log-rank test = 16.4, \( p < 0.001 \)). Compared with the low-risk group, patients in intermediate- and high-risk CHADS₂ subgroups had higher 5-year mortality (hazard ratio [HR]: 2.22 [95% confidence interval {CI}: 1.78–2.77] and 3.66 [95% CI: 2.38–5.62], respectively), stroke recurrence (HR: 1.74 [95% CI: 1.09–2.79] and 1.71 [95% CI: 1.08–2.71], respectively), and cardiovascular events (HR: 1.78 [95% CI: 1.23–2.57] and 1.86 [95% CI: 1.30–2.67], respectively). Compared with the low-risk group, patients in the high-risk CHA₂DS₂-VASc subgroup also had higher 5-year mortality (HR: 3.56, 95% CI: 1.89–6.70), stroke recurrence (HR: 2.93, 95% CI: 1.30–6.61), and cardiovascular events (HR: 2.71, 95% CI: 1.49–4.95).

Conclusions: Prestroke CHADS₂ and CHA₂DS₂-VASc scores predict long-term stroke outcomes in non-AF patients with acute ischemic stroke. These scores may provide a simple way of stroke prognostic risk stratification among non-AF stroke patients.

GLOSSARY

AF = atrial fibrillation; ASTRAL = Acute Stroke Registry and Analysis of Lausanne; CI = confidence interval; HR = hazard ratio; NIHSS = NIH Stroke Scale; SSS = Scandinavian Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

The CHADS₂ score is a well-validated tool for the estimation of stroke risk in patients with atrial fibrillation (AF). The acronym is derived from the score’s 5 constituents: congestive heart failure [CHF], Hypertension, Age 75 years or older, Diabetes mellitus (1 point each), and prior Stroke or TIA (2 points).¹² Recently, the CHA₂DS₂-VASc score (Congestive heart failure, Hypertension, Age 75 years or older, Diabetes mellitus, previous Stroke/TIA, Vascular disease, Age 65–74 years, Sex category) was introduced to complement the CHADS₂ score by being more inclusive of common stroke risk factors and improving the precision of identifying “low-risk” patients with AF who do not need any antithrombotic therapy.³
Most of the individual components of the CHADS2 and CHA2DS2-VASc scores have previously been shown to be associated with stroke prognosis. As expected, the CHADS2 score itself is associated with several aspects of stroke outcome such as early neurologic deterioration, stroke mortality, and 3-month clinical outcome after IV thrombolysis in patients with acute ischemic stroke and nonvalvular AF. However, the 5 components of the CHADS2 score are associated with stroke outcome not only in patients with AF but also in the general stroke population. This aspect has not been previously tested in a large cohort with long follow-up.

We hypothesized that the CHADS2 and CHA2DS2-VASc scores may be independently associated with recurrent stroke, cardiovascular outcomes, and death not only in stroke patients with AF, but also in non-AF patients. We tested this hypothesis in the Athens Stroke Registry, where we investigated whether CHADS2 or CHA2DS2-VASc score can predict stroke outcome in patients without AF.

METHODS The study population was derived from the Athens Stroke Registry, which includes all consecutive patients with an acute first-ever ischemic stroke admitted in Athens University Hospital, Athens, Greece, between January 1993 and December 2011 within 24 hours after stroke onset (or last proof of well-being in case of unknown-onset or wake-up stroke). Patients with TIA or recurrent stroke are not registered. All patients were admitted from the emergency department and treated in the acute stroke unit or in general medical wards. Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, current medication, time of stroke onset and hospital admission, duration of hospitalization, stroke characteristics, clinical findings and vital signs on admission, laboratory investigations, and administered treatment. Stroke severity was assessed by means of the Scandinavian Stroke Scale (SSS) during the 1993–1998 period, and the NIH Stroke Scale (NIHSS) score afterward. SSS was converted to NIHSS with the following previously validated formula: NIHSS = 25.68 – (0.43 × SSS). Stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Patients were prospectively followed up at 1, 3, and 6 months after discharge and yearly thereafter. Follow-up was routinely performed in the outpatient clinic. In case of patients with severe handicap, clinical follow-up was assessed at the patient’s residence or by telephone interview.

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 receiving antihypertensives. Diabetes mellitus was defined as patient already receiving anti diabetic drugs and/or insulin, or if fasting blood glucose level was >6.0 mmol/L before stroke. Dyslipidemia was defined as cholesterol concentration >6.5 mmol/L the day after admission, or if patient had a previous diagnosis of dyslipidemia. 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. To meet the case definition of heart failure, patients had to have typical symptoms (shortness of breath, fatigue, tiredness) with clinical signs of fluid retention (pulmonary or peripheral) and objective evidence of structural or functional abnormality of the heart at rest (i.e., cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, or increased natriuretic peptide concentration). TIA was defined as complete disappearance of signs and symptoms within 24 hours, regardless of infection being shown on neuroimaging. Stroke was defined according to World Health Organization criteria.

Patients with AF were excluded from this analysis. To assess the cardiac rhythm, we performed 12-lead EKG at admission, repeated EKGs during hospital stay, and/or continuous EKG monitoring for several days for patients treated in the stroke unit, and/or 24-hour Holter EKG monitoring (especially when AF was strongly suspected from the clinical presentation and brain imaging findings). Also, all patients were evaluated by a cardiologist. Patients who were included in the analysis were classified into subgroups according to their prestroke CHADS2 and CHA2DS2-VASc scores (low risk = 0, intermediate risk = 1, high risk = ≥2). The outcomes were death, stroke recurrence, and a composite of recurrent stroke, new myocardial infarction or unstable angina, aortic aneurysm rupture, peripheral embolism, and sudden death during the follow-up. The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee.

Statistical analysis. Continuous data are summarized as mean value and SD, and categorical as absolute numbers and proportion. The probability of 5-year survival in the CHADS2 and CHA2DS2-VASc subgroups was estimated using the Kaplan-Meier product limit method. Differences in Kaplan-Meier curves among the 3 groups were evaluated with the log-rank test. For patients lost during follow-up, survival data were censored at the last time known to be alive. Patients who experienced ≥1 composite vascular event during the follow-up period were censored at the time of the first event.

In the univariate analysis of the CHADS2 and CHA2DS2-VASc subgroups, dichotomous or categorical variables were compared using the χ² test and continuous variables with the analysis of variance test. The variables studied were age, sex, onset to admission time, stroke severity (assessed by the NIHSS score), stroke subtype by TOAST mechanism, cardiovascular risk factors and comorbidities (history of hypertension, diabetes, smoking, dyslipidemia, heart failure, ischemic heart diseases, peripheral vascular diseases, previous thromboembolism, TIA), prestroke medication (antiplatelets, antihypertensives, statins), treatment during hospitalization (thrombolysis, aspirin, anticoagulants), and recommended treatment at discharge (antiplatelets, warfarin, antihypertensives, statins). All parameters that were significant in the univariate analysis at p < 0.1 level (to decrease the risk of type II errors) were included in a multivariate Cox proportional hazards model to identify predictors of 5-year mortality and composite event. Associations are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). The level of statistical significance was set at 95%. The Statistical Package for Social Sciences version 15.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis.

RESULTS Among 3,133 patients admitted between January 1993 and December 2011, 461 (14.7%) and 916 (29.2%) were excluded from the analysis because
of intracranial hemorrhage and AF, respectively. Among 1,757 patients (mean age 67.2 ± 12.3 years, 68.2% males) who were finally included in the analysis, there were 262 (14.9%), 617 (35.3%), and 878 (50.0%) patients with low, intermediate, and high CHADS2 score, respectively. The corresponding numbers for CHA2DS2-VASc subgroups were 114 (6.3%), 252 (14.5%), and 1,391 (79.2%), respectively. The baseline characteristics of patients are summarized in table e-1 on the Neurology® Web site at www.neurology.org. The distribution of the CHADS2 and CHA2DS2-VASc scores among patients is presented in figures e-1 and e-2. The most common parameter in patients with a score of 1, 2, or 3 was arterial hypertension.

During the median follow-up of 33 months (interquartile range: 6–60 months), there were 388 composite cardiovascular events in 368 different patients: in particular, there were 232 recurrent strokes, 109 coronary artery events (i.e., acute myocardial infarction or unstable angina pectoris), 7 cases of peripheral artery disease, 6 aortic aneurysm ruptures, and 34 sudden deaths. The cumulative probability of 5-year survival was significantly different between the 3 CHADS2 subgroups: 79.0% (95% CI: 75.7%–82.3%) for the low-risk group, 60.6% (95% CI: 56.3%–64.9%) for the intermediate-risk group, and 44.5% (95% CI: 33.1%–55.9%) for the high-risk group (log-rank test 19.4, p < 0.0001; figure 1). Similarly, the cumulative probability of 5-year survival was significantly different between the 3 CHA2DS2-VASc subgroups: 87.8% (95% CI: 80.6%–95.1%) for the low-risk group, 85.4% (95% CI: 80.1%–90.7%) for the intermediate-risk group, and 64.0% (95% CI: 60.8%–67.1%) for the high-risk group (log-rank test 44.1, p < 0.0001; figure 1).

In the multivariate Cox proportional hazards model, both scores were independently associated with 5-year survival (tables 1 and 2). The reported adjustments in tables 1 and 2 correspond to the variables that were significant in the univariate analysis but were not significant in the multivariate analysis.

The cumulative probability of 5-year stroke recurrence was also significantly different between the CHADS2 subgroups (log-rank test 12.3, p = 0.002; figure 2) and between the CHA2DS2-VASc subgroups (log-rank test 10.6, p = 0.005; figure 2). In the multivariate Cox proportional hazards model, both scores were independently associated with 5-year stroke recurrence (tables 1 and 2).

The cumulative probability of 5-year cardiovascular events was significantly different between the CHADS2 subgroups (log-rank test 19.4, p < 0.001; figure 3) and between the CHA2DS2-VASc subgroups (log-rank test 16.4, p < 0.001; figure 3). In the multivariate Cox proportional hazards model, both scores were independently associated with 5-year cardiovascular events (tables 1 and 2).

**DISCUSSION** The present study in a large cohort with long follow-up shows that the CHADS2 and CHA2DS2-VASc scores are independent predictors of long-term outcome in patients with acute ischemic stroke but without AF. Indeed, patients with prestroke CHADS2 or CHA2DS2-VASc scores of 0 had lower rates of mortality, stroke recurrence, and cardiovascular events compared with patients in the high-risk subgroups. These scores may provide a simple means of stroke-risk stratification, even in non-AF patients with stroke.

The role of the CHADS2 score in the determination of long-term mortality risk of non-AF stroke patients was also evaluated recently in the Swedish Stroke Registry. Our study confirms these results because in our cohort, the cumulative probability of 5-year survival was 79.0% in the low-risk CHADS2 group and 60.6% in the intermediate-risk subgroup, which are similar to the Swedish Stroke registry (81% and 62%, respectively). Compared with this previous study, the present work extends the predictive role of CHADS2 score to also include the outcomes of stroke recurrence and overall cardiovascular risk in non-AF stroke patients, and also identifies a similar role for the CHA2DS2-VASc score.

The CHADS2 and CHA2DS2-VASc scores were originally introduced as tools to predict stroke risk in patients with AF. From this point of view, the results of the present study showing that they may also predict outcome in acute ischemic stroke patients without AF may come as a surprise. However, this can be easily explained when considering that most of the components of the CHADS2 and CHA2DS2-VASc scores were previously shown to be associated with prognosis in patients with acute stroke. In particular, heart failure was also shown to be associated with worse outcome in patients with acute stroke irrespective of the presence of AF. A history of hypertension was shown to be one of the significant predictors of recurrent stroke and cardiovascular events in patients with acute ischemic stroke. Moreover, age is a significant predictor of stroke outcome as previously shown with several risk scores and, more recently, with the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) score. Diabetes was shown to contribute directly to unfavorable outcome in patients with acute ischemic stroke. Finally, previous stroke and/or prestroke disability was also shown to be directly associated with short- and long-term mortality in patients with acute ischemic stroke. Therefore, the existence of all these parameters in the CHADS2 and CHA2DS2-VASc scores explains the good performance of the scores to predict stroke outcome. In a recent study, continuous monitoring identified newly diagnosed AF in 30% of patients with stroke risk factors. Whether patients with CHADS2...
risk factors but without a history of AF might benefit from implantable monitors for the selection and administration of anticoagulation for primary stroke prevention merits additional investigation.

There was no significant difference between the low- and intermediate-risk CHA2DS2-VASc subgroups in the multivariate analyses of the end points. This is probably explained by the distribution of the CHA2DS2-VASc scores being skewed to the right, i.e., skewed toward higher scores, and as a result, the low- and intermediate-risk subgroups are of much smaller size than the high-risk subgroups. In particular,
The low-, intermediate-, and high-risk CHA2DS2-VASc subgroups include 114, 252, and 1,391 patients, respectively. On the contrary, the distribution of the CHADS2 scores is less skewed toward higher scores (262, 617, and 878 patients in the 3 CHADS2 subgroups, respectively) and as a result, the differences in sample size between the 3 groups are relatively smaller. Because of this imbalance in the size of the subgroups, the CI so ft h eC H A2DS2-VASc multivariate analysis are wider compared with the CHADS2 analysis, which probably results in the lack of difference between the low- and intermediate-risk CHA2DS2-VASc subgroups.

### Table 1

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>5-y mortalityb</th>
<th>5-y stroke recurrencec</th>
<th>5-y composite cardiovascular eventsd</th>
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<tr>
<td>Low risk: CHADS2 0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate risk: CHADS2 1</td>
<td>2.22 (1.78-2.77)</td>
<td>2.30 (1.37-3.88)</td>
<td>2.08 (1.41-3.08)</td>
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<tr>
<td>High risk: CHADS2 ≥2</td>
<td>3.66 (2.38-5.62)</td>
<td>2.23 (1.34-3.72)</td>
<td>2.15 (1.47-3.15)</td>
</tr>
</tbody>
</table>

**TOAST subtype**

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<table>
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<tr>
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<tr>
<td>Lacunar</td>
<td>1.00</td>
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<td>Atherosclerotic</td>
<td>1.14 (0.80-1.60)</td>
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<td>Cardioembolic</td>
<td>2.56 (1.76-3.72)</td>
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<td>2.62 (1.92-3.57)</td>
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<td>Other/rare</td>
<td>0.94 (0.46-1.91)</td>
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<td>NIHSS score</td>
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<tr>
<td>Smoking</td>
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<td>0.75 (0.56-0.99)</td>
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<td>Coronary artery disease</td>
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<tr>
<td>Dyslipidemia</td>
<td>0.64 (0.52-0.79)</td>
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</tbody>
</table>

**Abbreviations:** NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

* Numbers represent hazard ratio (95% confidence interval).
* Adjusted for smoking and prior use of diuretics, calcium channel blockers, and statins.
* Adjusted for NIHSS score and TOAST subgroup.
* Adjusted for NIHSS score, TOAST subgroup, and smoking.

The low-, intermediate-, and high-risk CHA2DS2-VASc subgroups include 114, 252, and 1,391 patients, respectively. On the contrary, the distribution of the CHADS2 scores is less skewed toward higher scores (262, 617, and 878 patients in the 3 CHADS2 subgroups, respectively) and as a result, the differences in sample size between the 3 groups are relatively smaller. Because of this imbalance in the size of the subgroups, the CIs of the CHA2DS2-VASc multivariate analysis are wider compared with the CHADS2 analysis, which probably results in the lack of difference between the low- and intermediate-risk CHA2DS2-VASc subgroups.

### Table 2

<table>
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<tr>
<th>CHA2DS2-VASc score</th>
<th>5-y mortalityb</th>
<th>5-y stroke recurrencec</th>
<th>5-y composite cardiovascular eventsd</th>
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</thead>
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<tr>
<td>Low risk: CHA2DS2-VASc 0</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Intermediate risk: CHA2DS2-VASc 1</td>
<td>1.42 (0.69-2.93)</td>
<td>1.96 (0.80-4.75)</td>
<td>1.85 (0.96-3.57)</td>
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<tr>
<td>High risk: CHA2DS2-VASc ≥2</td>
<td>3.56 (1.89-6.70)</td>
<td>2.93 (1.30-6.61)</td>
<td>2.71 (1.49-4.95)</td>
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</tbody>
</table>

**TOAST subtype**

<p>| | | |</p>
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<td>Cardioembolic</td>
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<td>Other/rare</td>
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<tr>
<td>NIHSS score</td>
<td>1.08 (1.07-1.09)</td>
<td>—</td>
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<tr>
<td>Dyslipidemia</td>
<td>0.63 (0.51-0.78)</td>
<td>—</td>
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</table>

**Abbreviations:** NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

* Numbers represent hazard ratio (95% confidence interval).
* Adjusted for smoking and prior use of diuretics, calcium channel blockers, and statins.
* Adjusted for NIHSS score, TOAST subgroup, and smoking.
As shown from the results of the multivariate analyses of both scores, dyslipidemia was inversely associated with 5-year stroke mortality. A meta-analysis of 61 prospective studies with 55,000 vascular deaths did not confirm an independent positive association between dyslipidemia and stroke mortality.21 Similar results were also shown in previous studies.22 Stroke is a heterogeneous syndrome with different etiologic subtypes (e.g., large-artery atherosclerosis, small-vessel disease, and cardioembolic), and a positive association between dyslipidemia and stroke outcome may be missed when all stroke subtypes are studied together. In the multivariate analysis of the CHADS2 score, smoking was found to have a paradoxical protective effect on stroke recurrence, of borderline significance. This seems similar to the
paradoxical association between smoking and survival after acute myocardial infarction—the “smoker’s paradox”\textsuperscript{23}—but these results may represent a type I error.

Several prognostic risk scores have been introduced to predict stroke outcome. Recently, the ASTRAL score was shown to predict functional outcome (assessed with the modified Rankin Scale score) at 3 months in patients with acute ischemic stroke. The ASTRAL score includes 6 readily available parameters, i.e., age, stroke severity (assessed with the NIHSS score), time delay between stroke onset and hospital admission, presence of visual field defect, glucose at admission, and level of consciousness. The iScore was initially shown to predict mortality at 30 days and at 1 year, and disability at 30 days after acute ischemic stroke. Another prognostic score validated in the VISTA database was recently shown to make
a reliable prediction of survival and functional outcome at 3 months after ischemic stroke. The main difference with these prognostic scores is that the CHADS2 and CHA2DS2-VASc scores do not predict functional outcome but are related to overall cardiovascular risk. The prognostic ability of the CHADS2 and CHA2DS2-VASc scores compared with the aforementioned scores merits further analysis.

The main strengths of the present study include the assessment of hard clinical outcome measures such as mortality, stroke recurrence, and cardiovascular events, the long follow-up of patients, and the large sample size of consecutive patients registered within a wide time window of 19 years. However, the study has several limitations that need to be acknowledged. First, this study is characterized by the inherent limitations of any retrospective study of prospectively collected data such as collection and entry bias, and possible residual confounding. Also, patients admitted with TIA or recurrent stroke are not registered in our analysis because they are not registered in our registry. In addition, this is a hospital-based study, which may introduce selection bias, and therefore these results need to be confirmed in population-based studies. Moreover, other potential confounders were not assessed, such as adherence to secondary prevention regimens (e.g., antihypertensives, lipid-lowering drugs, antiplatelets). Finally, although we regularly assessed patients’ cardiac rhythm by using 24-hour EKG monitoring in the stroke unit and 24-hour Holter monitoring for selected patients with suspected AF, it is possible that some patients with paroxysmal AF may have been missed and wrongly diagnosed as sinus rhythm, and therefore may have influenced outcome.

In conclusion, prestroke CHADS2 and CHA2DS2-VASc scores predict long-term stroke outcomes in a large cohort of patients with acute ischemic stroke but without AF. These simple scores may provide a means of easy clinical stroke prognostic risk stratification, even among non-AF patients with stroke.

AUTHOR CONTRIBUTIONS
Dr. Ntaios, Dr. Lip, Dr. Vemmos: study concept and design. Dr. Vemmos, Dr. Vemmou, Dr. Koroboki, Dr. Savvari, Dr. Manios: acquisition of data. Dr. Ntaios, Dr. Vemmos, Dr. Papavasileiou: analysis and interpretation. Dr. Ntaios, Dr. Lip, Dr. Makarinis, Dr. Vemmos, Dr. Milionis: critical revision of the manuscript for important intellectual content. Dr. Ntaios, Dr. Lip, Dr. Vemmos: study supervision.

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DISCLOSURE
The authors report no disclosures. Go to Neurology.org for full disclosures.


REFERENCES


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