

CHA₂DS₂-VASc score as a predictor of long-term cardiac outcomes in elderly patients with or without atrial fibrillation

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Background: The CHA₂DS₂-VASc score is often used for stroke risk stratification in atrial fibrillation (AF) patients. However, its usefulness in patients ≥ 75 years of age with or without AF is unclear.

Objective: We aimed to investigate whether the CHA₂DS₂-VASc score can predict ischemic stroke (IS), transient ischemic attack, thromboembolism (TE), and mortality in elderly patients with and without AF.

Materials and methods: During 2013–2014, 1,071 patients (36.3% with concomitant AF) at least 75 years old were enrolled, and the follow-up ended on July 15, 2017. Variables included sociodemographic characteristics, complications, drugs taken, laboratory results, and echocardiographic parameters. The primary end points were IS, transient ischemic attack, and TE, expressed as IS/TE. All-cause mortality was a secondary end point. Survival curves and mortality risks were assessed via Kaplan–Meier survival analysis and compared by log-rank tests.

Results: The average follow-up duration was 2.57 ± 1.37 years. Overall, 167 patients (5.6%) died and 77 (7.2%) developed IS/TE. The CHA₂DS₂-VASc score was associated with IS/TE in patients 75 years or older with and without AF, and patients with a CHA₂DS₂-VASc score ≥ 5 had a higher risk of stroke. However, the CHA₂DS₂-VASc score was not related to all-cause mortality.

Conclusion: The CHA₂DS₂-VASc score can predict IS/TE, but not mortality, in elderly patients (≥ 75 years) with or without AF.

Keywords: CHA₂DS₂-VASc score, atrial fibrillation, elderly, stroke, survival

Introduction

Age is associated with increased risks of stroke and mortality in patients with either atrial fibrillation (AF) or sinus rhythm.¹ Measures to identify individuals with an elevated risk of stroke would facilitate the early application of prevention strategies, and thus, reliable stroke risk prediction schemes are urgently needed.

The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years [double score], diabetes, prior stroke or transient ischemic attack [TIA; double score], vascular disease, age 65–74 years, sex class [female]) scoring system has gained prominent status as a key prediction tool for stroke risk stratification in patients with AF.² In recent years, the value of the CHA₂DS₂-VASc score for predicting ischemic stroke (IS) and mortality has been shown to extend beyond the original field to heart failure and myocardial infarction.^{3–5} In this study, we hypothesized that the CHA₂DS₂-VASc score can also predict IS and mortality in elderly patients with or without AF.

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Materials and methods

A retrospective study was conducted by enrolling consecutive patients aged 75 years or older at Beijing Friendship Hospital between January 1, 2013 and December 31, 2014. The data for all individual patients could be retrieved as all data at our hospital are linked to a unique permanent registration number. Diagnosis of AF was based on electrocardiography, 24-hour Holter monitoring, or the patient's medical history of AF.^{6,7} We excluded patients with mechanical prosthetic heart valves, pulmonary embolism, or recent deep vein thrombosis and intraventricular thrombus. Patients who had been on oral anticoagulation therapy within the previous 3 months were excluded from the study.

Ethical approval was obtained from the Ethical Committee of Beijing Friendship Hospital, and all patients provided written informed consent to participate in this research study.

Follow-up was performed by reviewing data in medical records or from telephone interviews that were available in the hospital database. Data collected during the follow-up period, which started from the enrollment date and ended on July 15, 2017, were used to assess the risk of TIA, IS, thromboembolism (TE), and death.

Risk stratification using CHA₂DS₂-VASc score

The CHA₂DS₂-VASc score was calculated for each patient according to the current clinical guidelines. The score ranges from 0 to 9 points and includes the following clinical characteristics: congestive heart failure or left ventricular dysfunction (1 point), hypertension (1 point), age ≥ 75 years (2 points), diabetes (1 point), stroke/TIA (2 points), vascular disease (1 point), age 65–74 years (1 point), and sex category (female; 1 point). The sum of all factors provides the individual patient's risk score.

Definition of end points

The primary end point was defined as a hospital diagnosis of IS, TIA, or TE (peripheral arterial embolism, pulmonary embolism). IS/TE presents IS, TIA, and TE events combined. All-cause death was included as a secondary end point.

IS was identified by a new, sudden focal neurological deficit with a presumed cerebrovascular cause that persisted for 24 hours and could not be attributed to other identifiable causes. Events that involved symptoms and lasted < 24 hours were considered as TIA. Brain imaging was performed to distinguish hemorrhagic stroke from IS. Peripheral artery embolism was defined as abrupt vascular insufficiency associated with clinical or radiographic evidence of peripheral

arterial occlusion in the absence of other likely causes. The presence of vascular disease was identified from previous diagnoses, including myocardial infarction, peripheral artery disease, and complex aortic plaque.

Statistical analysis

Statistical analysis was carried out using the software SPSS, version 16.0 (IBM Corp., Armonk, NY, USA).

The baseline characteristics of the patients are described using mean and standard deviation values for continuous measures and percentages for categorical measures. Univariate comparisons were made with the χ^2 or two-sample *t*-test. Post hoc analyses were performed using the Bonferroni test (Table 1). Time at risk was measured from the enrollment date to the time at which an IS, TIA, or TE event occurred, the date of death, or the end of the study (July 15, 2017). Time-to-event analysis was used to describe the association between the CHA₂DS₂-VASc score and the risk of IS/TE and death separately for the elderly patients with and without AF. The cumulative occurrence of major adverse outcomes was analyzed with the Cox proportional hazard regression model. Relative risks with 95% CIs are reported. Additionally, we measured the cumulative event-free survival by the Kaplan–Meier method and compared unadjusted differences using the log-rank test.

Table 1 Baseline characteristics of the patients according to prior diagnosis of AF

| Clinical characteristic | No (%) of patients | | P-value |
|--|-----------------------|--------------------|---------|
| | Without AF (n=682) | With AF (n=389) | |
| Female, n (%) | 466 (68.3%) | 298 (76.6%) | 0.004* |
| Age, years | 84.3 \pm 4.4 | 83.7 \pm 4.9 | 0.061 |
| Baseline comorbidity | | | |
| Hypertension | 679 (99.6%) | 317 (81.5%) | 0.000* |
| Vascular disease | 279 (40.9%) | 216 (55.5%) | 0.000* |
| Diabetes | 246 (36.7%) | 136 (36.1%) | 0.587 |
| Previous ischemic stroke | 11 (1.7%) | 138 (35.7%) | 0.000* |
| Heart failure | 128 (19.1%) | 96 (24.9%) | 0.027* |
| Baseline medication | | | |
| Antiplatelet drug | 346 (50.7%) | 255 (65.7%) | 0.001* |
| Calcium channel antagonists | 381 (55.9%) | 158 (40.5%) | 0.002* |
| Angiotensin-converting enzyme inhibitors | 30 (4.4%) | 42 (10.7%) | 0.005* |
| Angiotensin receptor blockers | 279 (40.9%) | 135 (34.7%) | 0.398 |
| β -blocker | 181 (26.6%) | 177 (45.5%) | 0.000* |
| Cr (mg/dL) | 90.08 \pm 47.98 | 100.87 \pm 59.71 | 0.030* |
| LA (mm) | 35.91 \pm 5.64 | 40.48 \pm 10.17 | 0.000* |
| EF (%) | 64.44 \pm 7.50 | 62.08 \pm 9.30 | 0.003* |
| CHA ₂ DS ₂ -VASc | 4.60 \pm 1.31 | 4.87 \pm 1.41 | 0.002* |

Note: * $P < 0.05$.

Abbreviations: AF, atrial fibrillation; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or TIA (transient ischemic attack), vascular disease, age 65–74 years, sex class; Cr, creatinine; LA, left atrium; EF, ejection fraction.

The diagnostic utility of the CHA₂DS₂-VASc score for detecting major adverse outcomes was determined via receiver-operating characteristic curve analysis. The results are expressed using the concordance (c) statistic. The significance level was set at $P < 0.05$.

Results

Between January 1, 2013 and December 30, 2014, we screened 1,200 consecutive patients, and 139 of them met at least one of the exclusion criteria. The remaining 1,071 patients were eligible and included in the study protocol. They were followed through medical records or telephone contact for 0.04–5.67 years, with a mean follow-up duration of 2.57 ± 1.37 years.

The baseline characteristics of the patients categorized as with or without AF are presented in Table 1. Compared to those without AF, patients with AF had more cardiovascular comorbidities: heart failure (24.9% vs 19.1%), vascular disease (55.5% vs 40.9%), and previous IS (35.7% vs 17.2%). Patients with AF had a lower ejection fraction ($62.08\% \pm 9.30\%$ vs $64.44\% \pm 7.50\%$, $P = 0.003$), bigger left atrium (40.48 ± 10.17 vs 35.91 ± 5.64 mm, $P < 0.001$), and creatinine (100.87 ± 59.71 vs 90.08 ± 47.98 mg/dL, $P = 0.03$). The mean CHA₂DS₂-VASc score was 4.7 ± 1.4 , and AF patients had higher scores than patients without AF.

After an average follow-up of 2.57 ± 1.37 years, 77 IS/TE events occurred among the study population. Also, there were 167 all-cause deaths, and among them, 68 patients died of pneumonia, 40 of cancer, 56 of cardiovascular disease, and three of other diseases. Overall, the incidence of major adverse cardiovascular end points was 3.2 per 100 person-years. AF increased the incidence of IS/TE significantly (log-rank = 22.62, $P = 0.000$) and had no effect on all-cause mortality (log-rank = 3.66, $P = 0.056$; Figure 1).

The incidence rates of different events during the follow-up are listed in Table 2. For the combined ischemic outcome including IS, TIA, and TE, the incidence rate was significantly higher among patients with AF than in those without AF in comparisons of those with CHA₂DS₂-VASc scores of 2, 3, 4, 5, and ≥ 6 (with concomitant AF: 0%, 4.05%, 3.5%, 10.22%, and 12.20%, respectively, and without AF: 0%, 0.89%, 2.47%, 3.21%, and 1.14%, respectively). For all-cause death, the incidence rate did not increase significantly with increasing CHA₂DS₂-VASc score (with concomitant AF: 31.60%, 10.24%, 9.78%, 13.44%, and 14.71%; without AF: 0%, 19%, 18.25%, 16.5%, and 26.58% for scores 2, 3, 4, 5, and ≥ 6 , respectively; Table 2).

The discriminatory properties of the CHA₂DS₂-VASc score depended on the choice of end point (Figure 2). The CHA₂DS₂-VASc score showed obvious predictive ability for

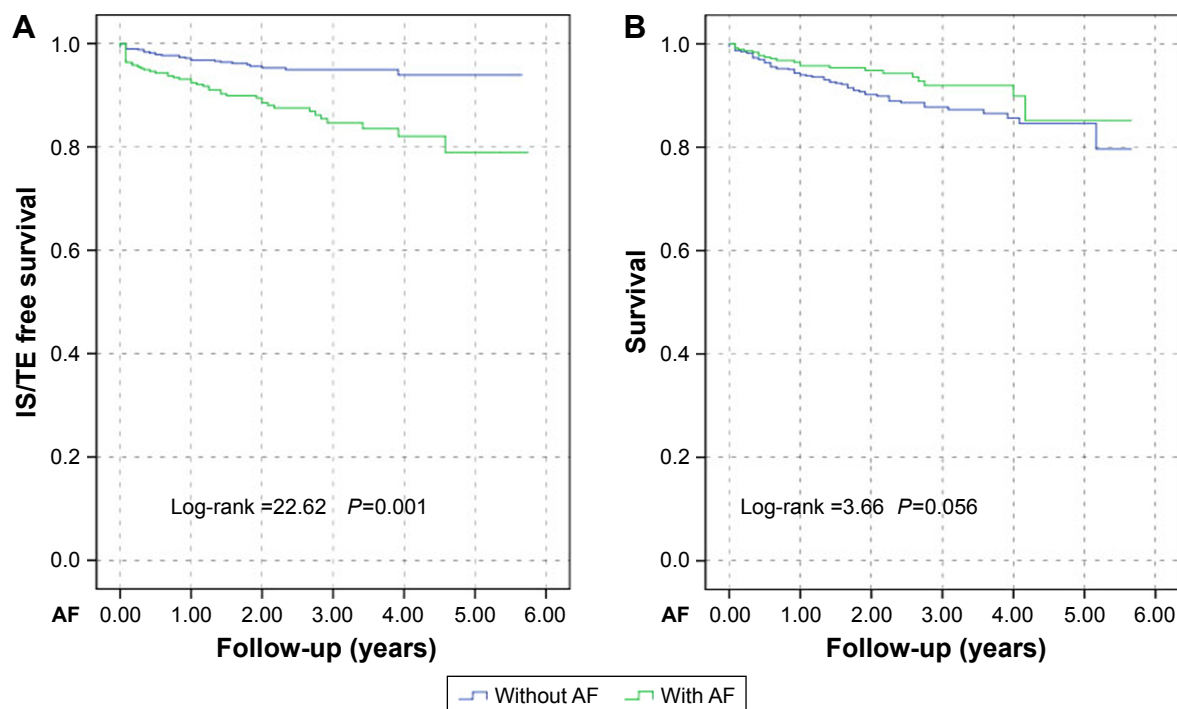


Figure 1 Kaplan-Meier survival curves for ≥ 75 year-old patients with and without AF.

Notes: (A) AF significantly increased the risk of IS, TIA, and TE. (B) AF had no significant effect on all-cause mortality.

Abbreviations: AF, atrial fibrillation; IS, ischemic stroke; TE, thromboembolism; TIA, transient ischemic attack.

Table 2 Incidence of IS/TE and death during follow-up in ≥ 75 year-old patients with and without AF

| End point | Overall | CHA ₂ DS ₂ -VASc score | | | | |
|-----------------------------------|---------|--|-------|-------|-------|----------|
| | | 2 | 3 | 4 | 5 | ≥ 6 |
| Patients with AF, n | 389 | 3 | 71 | 99 | 84 | 132 |
| IS/TE | | | | | | |
| Events, n | 49 | 0 | 6 | 8 | 13 | 21 |
| Person-years, n | 50.36 | 0 | 1.74 | 12.83 | 18.13 | 17.66 |
| Incidence (100 person-years) | 7.04 | 0 | 4.05 | 3.50 | 10.22 | 12.20 |
| Death | | | | | | |
| Events, n | 99 | 2 | 16 | 23 | 22 | 36 |
| Person-years, n | 113.23 | 0.33 | 14.33 | 36.37 | 26.58 | 35.62 |
| Incidence rate (100 person-years) | 12.28 | 31.60 | 10.24 | 9.78 | 13.44 | 14.71 |
| Patients without AF, n | 682 | 2 | 150 | 200 | 168 | 162 |
| IS/TE | | | | | | |
| Events, n | 28 | 0 | 3 | 10 | 11 | 4 |
| Person-years, n | 24.18 | 0 | 2.75 | 7.33 | 8.19 | 5.91 |
| Incidence (100 person-years) | 1.94 | 0 | 0.89 | 2.47 | 3.21 | 1.14 |
| Death | | | | | | |
| Events, n | 68 | 0 | 14 | 21 | 17 | 16 |
| Person-years, n | 80.33 | 0 | 19.0 | 18.25 | 16.50 | 26.58 |
| Incidence rate (100 person-years) | 4.68 | 0 | 4.15 | 5.03 | 4.98 | 4.60 |

Abbreviations: AF, atrial fibrillation; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or TIA (transient ischemic attack), vascular disease, age 65–74 years, sex class; IS, ischemic stroke; TE, thromboembolism.

the end point of IS/TE in the elderly patients ≥ 75 years of age (c statistic = 0.583, 95% CI, 0.518–0.647). The predictive ability of CHA₂DS₂-VASc score for the end point of IS/TE was a little better for the patients with AF than for those

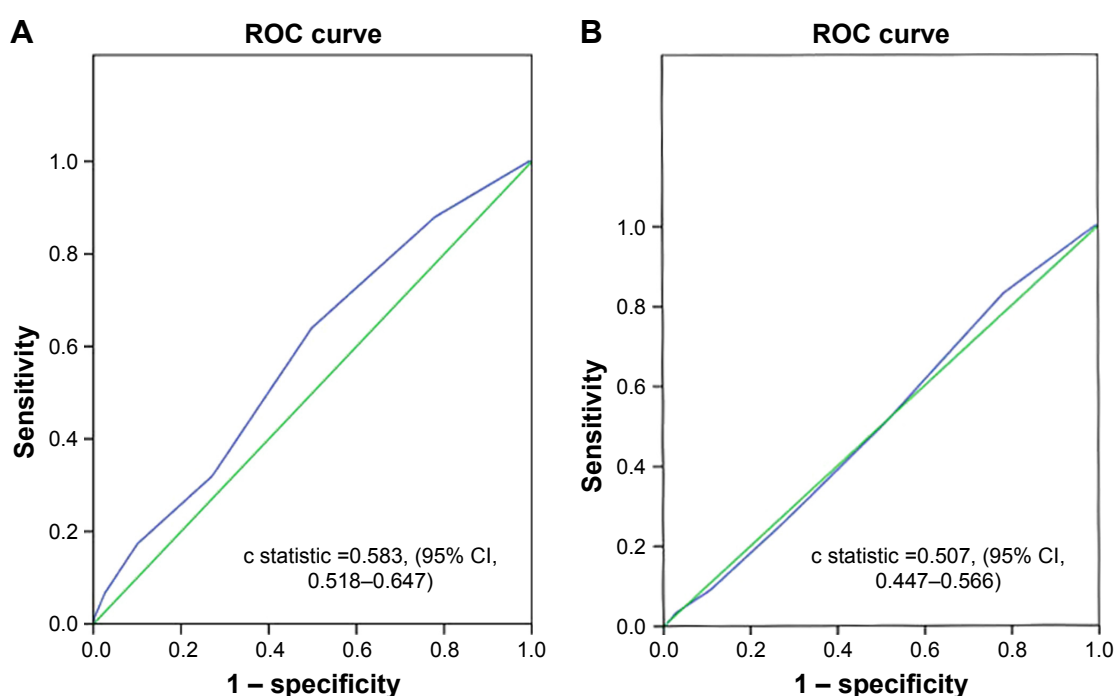
without AF (c statistic = 0.598, 95% CI, 0.513–0.683 vs c statistic = 0.529, 95% CI, 0.435–0.623, respectively). The CHA₂DS₂-VASc score had no significant predictive ability for all-cause death in patients either with or without AF (c statistic = 0.503, 95% CI, 0.432–0.579 vs c statistic = 0.515, 95% CI, 0.449–0.581, respectively).

According to the Cox regression models, hypertension and age were independently associated with all-cause death during long-term observation ($P < 0.05$), with 129% and 8.1% increases, respectively, during follow-up. Elderly age increased the stroke risk by 8.1% and mortality by 7.4%. Previous stroke and age were associated with IS/TE (Table 3).

For the patients over 75 years of age, the CHA₂DS₂-VASc score of 5 was the cut-off value with a sensitivity of 64% and a specificity of 50%. The incidence of IS/TE in patients with CHA₂DS₂-VASc score of ≥ 5 was 4.44 per 100 person-years vs 2.38 for those with a CHA₂DS₂-VASc score < 5 , with a relative risk of 1.87. Figure 3 shows the IS/TE event-free survival according to the CHA₂DS₂-VASc score. A CHA₂DS₂-VASc score ≥ 5 increased the incidence of IS/TE significantly.

Discussion

The CHA₂DS₂-VASc scores were originally developed for stroke risk stratification of patients with nonvalvular AF to guide individualized risk-reduction anticoagulation therapy, especially for patients identified as “low risk”.^{8–11} To date,

**Figure 2** (Continued)

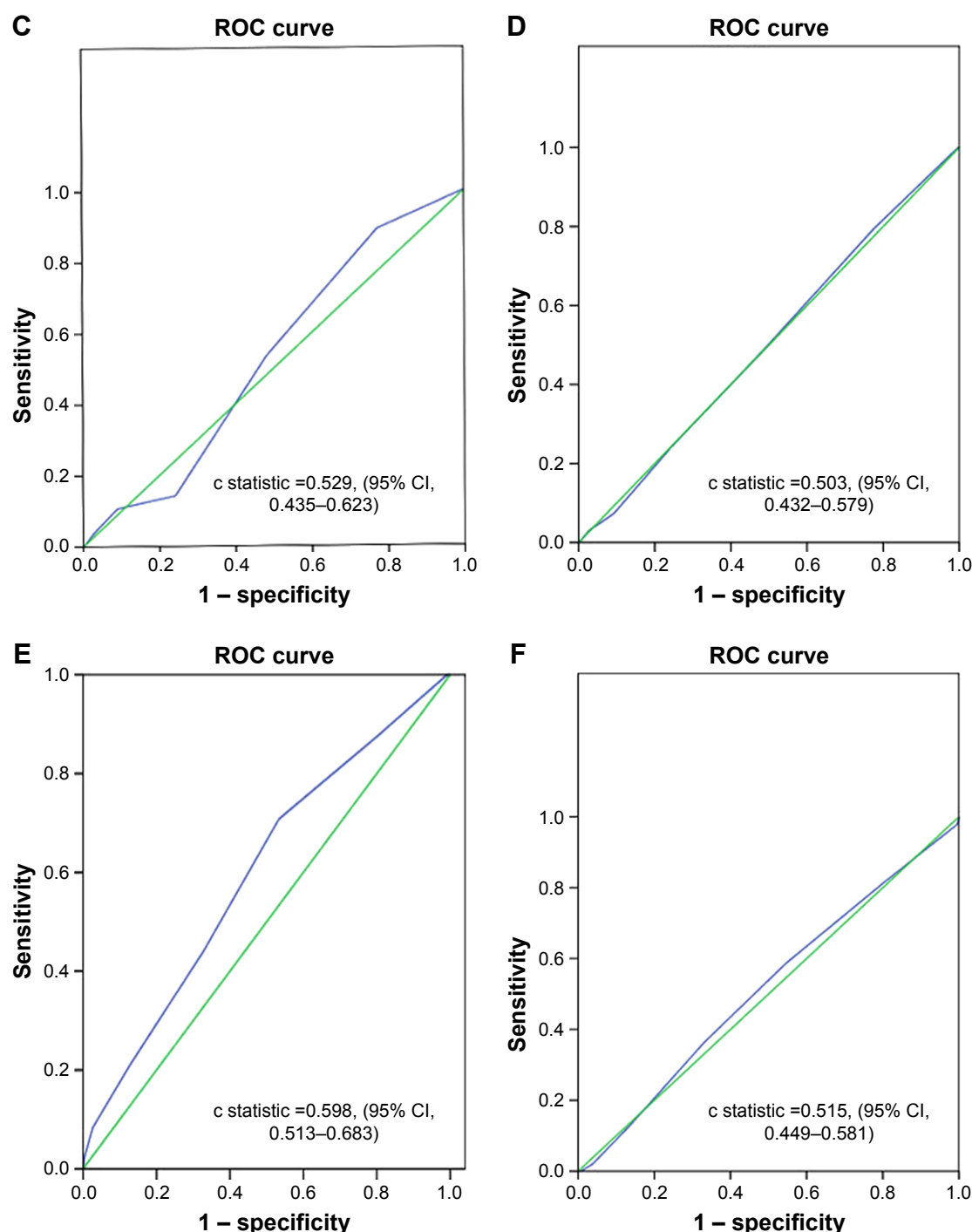


Figure 2 ROC curves for analysis of the value of the CHA₂DS₂-VAsC score for predicting the end points of IS/TE and death.

Notes: (A) IS/TE among the patients aged ≥ 75 years. (B) All-cause death among the elderly patients. (C) IS/TE for the patients without AF. (D) All-cause death for the patients without AF. (E) IS/TE for the patients with AF. (F) All-cause death among the patients with AF. The c statistics (area under the curve) with the 95% CIs are 0.583 (95% CI, 0.518–0.647), 0.507 (95% CI, 0.447–0.566), 0.529 (95% CI, 0.435–0.623), 0.503 (95% CI, 0.432–0.579), 0.598 (95% CI, 0.513–0.683), and 0.515 (95% CI, 0.449–0.581), respectively. In figure (E) the specificity: 0.640; sensitivity: 0.498; cut-off value of CHA₂DS₂-VAsC was 5.

Abbreviations: CHA₂DS₂-VAsC, congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or TIA (transient ischemic attack), vascular disease, age 65–74 years, sex class; IS, ischemic stroke; ROC, receiver-operating characteristic; TE, thromboembolism.

its value has been assessed in many patients without AF.^{12–14} Podolecki et al demonstrated that the CHA₂DS₂-VAsC score is strongly associated with in-hospital mortality in acute myocardial infarction patients.¹⁵ Melgaard et al found that for heart failure patients with or without AF, the CHA₂DS₂-VAsC

score is associated with the risks of IS and death.¹⁶ Polenz et al performed a prospective study of outpatients without AF or flutter and found that the CHA₂DS₂-VAsC score can predict major adverse cardiac outcomes, including stroke and death.⁵ However, whether the CHA₂DS₂-VAsC score

Table 3 Multivariate Cox proportional hazard analysis evaluating independent predictors of mortality and IS/TE events in ≥ 75 year-old patients with or without AF

| Parameter | Hazard ratio (95% CI) | Wald χ^2 | P-value |
|------------------------|-----------------------|---------------|---------|
| Risk factor for death | | | |
| Hypertension | 2.299 (1.479–3.573) | 13.684 | 0.000* |
| Previous stroke | 0.794 (0.557–1.132) | 1.625 | 0.202 |
| Age | 1.081 (1.048–1.114) | 25.152 | 0.000* |
| Heart failure | 0.923 (0.636–1.339) | 0.177 | 0.674 |
| Diabetes | 1.010 (0.731–1.394) | 0.003 | 0.954 |
| Female | 1.105 (0.776–1.574) | 0.307 | 0.579 |
| Vascular disease | 0.870 (0.630–1.200) | 0.723 | 0.395 |
| Risk factors for IS/TE | | | |
| Hypertension | 1.452 (0.710–2.966) | 1.045 | 0.307 |
| Previous stroke | 2.538 (1.568–4.107) | 14.383 | 0.000* |
| Age | 1.080 (1.031–1.080) | 10.722 | 0.001* |
| Heart failure | 1.333 (0.787–2.259) | 1.144 | 0.285 |
| Diabetes | 0.961 (0.592–1.560) | 0.00 | 0.992 |
| Female | 1.024 (0.613–1.709) | 0.008 | 0.928 |
| Vascular disease | 0.951 (0.589–1.536) | 0.042 | 0.837 |

Note: * $P \leq 0.001$.

Abbreviations: AF, atrial fibrillation; IS, ischemic stroke; TE, thromboembolism.

can predict stroke and embolism for patients of age at least 75 years irrespective of AF has not been reported.

Our study demonstrated that for patients aged 75 years or older, the CHA₂DS₂-VASc score was able to identify patients at high risk for stroke and could be used to quickly evaluate the stroke risk in both AF and non-AF populations, as suggested by Lip et al.⁸ Some mechanisms may explain the strong predictive value of CHA₂DS₂-VASc for the elderly patients without AF. First, all the involved risk factors were

shown to increase the stroke incidence not only in the AF population but also in patients without AF. Diabetes mellitus, hypertension, and congestive heart failure are associated with endothelial dysfunction, increased thrombin formation, and abundance of adhesion molecules, which all together lead to a prethrombotic state, thereby contributing to imbalance of procoagulants and anticoagulants.^{17–19} Secondly, a positive association was observed between the number of risk factors and the incidence rates of IS and TIA.²⁰ Our study had a high prevalence of cardiovascular diseases and relevant risk factors such as hypertension (93% of patients), diabetes (35.7%), heart failure (20.9%), and vascular disease (46.2%), which caused the high incidence of stroke.

Age and a previous stroke were independent risk factors for IS/TE events among the very old patients.²¹ In our study, a CHA₂DS₂-VASc score of 5 could easily separate individuals with a high risk of stroke from those at lower risk, with a sensitivity of 64% and a specificity of 50%. The incidence of IS/TE was 3-fold greater in patients with a CHA₂DS₂-VASc score ≥ 5 compared with that in patients with a score < 5 . As an independent predictor for stroke, the CHA₂DS₂-VASc score has the distinct advantage that it can be quickly calculated bedside. For those with higher scores, especially > 5 , we should strengthen antiplatelet therapy, especially with new oral anticoagulation.²² This therapy should also be applied in future studies to investigate the effect of prophylactic anticoagulation in high-risk patients without AF.²³

The CHA₂DS₂-VASc score showed no predictive value for mortality, consistent with the findings of Clua-Espuny et al²⁴ who found no association between death and AF for patients 80 years or older, and with chronic heart failure. The independent risk factors for annual mortality were male gender, enlarged left ventricular systolic dimension, and dyslipidemia. Notably, our study differed from those that reported an increased risk of mortality in AF patients (both in-hospital and long term) and in special patient populations such as those with heart failure, heart transplant recipients, and those with Takotsubo syndrome.^{25–27} First, different study populations may explain the different results. In our study, only 46.2% of patients suffered from heart disease. Instead, most of the patients died of pneumonia and cancer, with only 33.5% having died of myocardial infarction, stroke, or another cardiovascular disease. The CHA₂DS₂-VASc score only had a strong predictive value for the latter. Secondly, the mean patient age differed between this study and previous studies. Most previous studies enrolled middle-aged to elderly patients, whereas our patient population was aged from 75 to 100 years, much older than other studies.

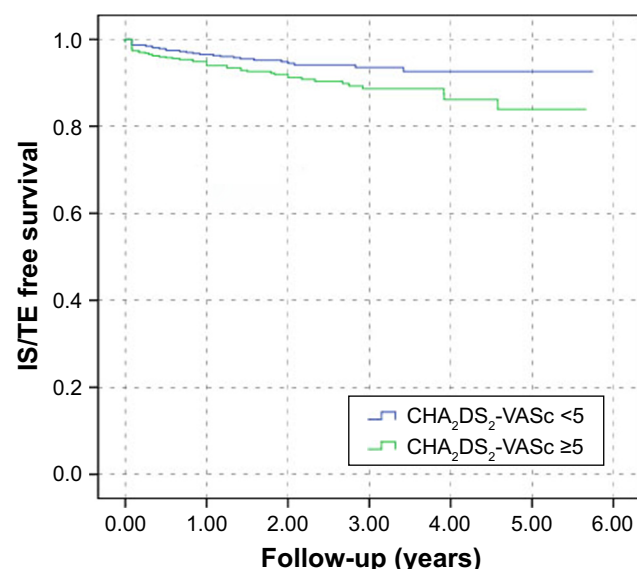


Figure 3 Kaplan–Meier survival curves for stratification of patients by the CHA₂DS₂-VASc score with a cut-off value of 5.

Note: A CHA₂DS₂-VASc score ≥ 5 increased the incidence of IS/TE significantly (log-rank = 5.548, $P = 0.019 < 0.05$).

Abbreviations: CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke or TIA (transient ischemic attack), vascular disease, age 65–74 years, sex class; IS, ischemic stroke; TE, thromboembolism.

Conclusion

The risk of TE was strongly associated with the CHA₂DS₂-VASc score for patients 75 years old or older with and without AF. Hence, this scoring system may be useful for identifying patients at high risk for stroke who have no history of AF and for whom additional preventive measures might be beneficial to improving outcomes.

Limitations of the study

Our study had several limitations. The results were derived from a single-center, retrospective study. The small sample size, short follow-up, and small number of events also represent a source of bias. The specificity and sensitivity of the CHA₂DS₂-VASc score for predicting cardiac events were not high, which is likely because the risk factors for patients without AF differ from those for patients with AF. Also, we did not consider different types of AF (paroxysmal, persistent, and permanent), and perhaps outcomes would have differed among these groups.

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Disclosure

The authors report no conflicts of interest in this work.

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