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Pre-stroke CHA₂DS₂-VASc score and severity of acute stroke in patients with atrial fibrillation: findings from RAF study

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Abstract

Background and Purpose: The aim of this study was to investigate for a possible association between both pre-stroke CHA2DS2-VASc score and the severity of stroke at presentation as well as disability and mortality at 90 days in patients with acute stroke and atrial fibrillation (AF).

Methods: This prospective study enrolled consecutive patients with acute ischemic stroke, AF and assessment of pre-stroke CHA2DS2-VASc score. Severity of stroke was assessed at admission by the National Institute of Health Stroke Scale (NIHSS) score, (severe stroke: NIHSS≥10). Disability and mortality at 90 days were assessed by the modified Rankin Scale (mRS<3 or ≥3). Multiple logistic regression was used to correlate pre-stroke CHA2DS2-VASc and severity of stroke as well as disability and mortality at 90 days.

Results: Of the 1.020 patients included in the analysis, 606 patients had an admission NIHSS score lower and 414 patients higher than 10. At 90 days, 510 patients had mRS≥3. A linear correlation was found between pre-stroke CHA2DS2-VASc score and severity of stroke (p=0.001). On multivariate analysis, CHA2DS2-VASc score correlated with the severity of stroke (p=0.041) and adverse functional outcome (mRS≥3) (p=0.001). A logistic regression with the ROC graph procedure (C statistic) evidenced an area under the curve of 0.60 (p=0.0001) for severe stroke. Furthermore, a correlation was found between pre-stroke CHA2DS2-VASc score and the lesion size.

Conclusions: In patients with AF, in addition to the risk of stroke, a high CHA2DS2-VASc score was independently associated with both stroke severity at onset and disability and mortality at 90 days.
Background and Purpose

In patients with atrial fibrillation (AF), current guidelines recommend using the CHA2DS2-VASc score to assess the risk of stroke\(^1\). In retrospective studies CHA2DS2-VASc score have been suggested as a predictor of severity of stroke at admission and poor outcome\(^2-4\).

The aim of this study was to investigate for a possible association between both pre-stroke CHA2DS2-VASc score and the severity of stroke at presentation as well as disability and mortality at 90 days in patients with acute stroke and atrial fibrillation (AF).

Methods

Data for this analysis were extracted from the database of a prospective multicentre study which had enrolled consecutive patients with acute stroke and AF (the RAF study)\(^5\). This study, carried out between January 2012 and March 2014, enrolled 1,029 consecutive patients from 29 Stroke Units throughout Europe and Asia.

Pre-stroke CHA2DS2-VASc score was evaluated as previously described\(^5\). On admission, the severity of acute stroke was assessed using the National Institutes of Health Stroke Scale (NIHSS); all investigators were certified on the use of this scale. Disability and mortality at 90 days were assessed using the modified Rankin Scale (mRS).

Data on known stroke risk factors were collected as reported in the main paper\(^5\).

A cerebral computed tomography (CT) or magnetic resonance (MR) was performed on admission for all patients to exclude intracranial hemorrhage. A second cerebral CT scan or MR was performed 48-72 h from stroke onset. The sites and sizes of the qualifying infarcts were determined based on standard templates\(^6,7\) as previously described\(^5\).

Statistical analysis

The primary pre-specified a priori study question was if CHA2DS2-VASc score had been associated with stroke severity assessed by NIHSS at onset. Then, as a post-hoc analysis,
possible correlations between CHA2DS2-VASc scores and outcome assessed by mRS and between CHA2DS2-VASc scores and lesion size were investigated for.

The admission NIHSS score was evaluated both as a continuous variable for the correlation coefficient r analysis, and dichotomized variables (severe stroke NIHSS≥10) for the multivariate analysis.

The correlation coefficient r, Pearson product-moment correlation coefficient, was used to measure the strength of the linear association between CHA2DS2-VASc before the event and NIHSS score on admission (as continuous variable).

Correlations between pre-stroke CHA2DS2-VASc and severity of stroke were sought by multiple logistic regression after adjusting for the following variables: smoking, hyperlipidemia, alcohol abuse and use of statins in addition to CHA2DS2-VASc.

Thereafter, the probability of a receiver-operating characteristic (ROC) curve against NIHSS≥10 as dependent variable was plotted. The area under this curve suggests an ability of the CHA2DS2-VASc score to predict for severe stroke, which is also referred to as the C-statistic (Harrell’s C).

In addition, a multiple logistic regression model including components singularly of the CHA2DS2-VASc was performed.

Stroke was defined as either non-disabling (mRS 0 to 2) or disabling (mRS 3 to 5).

The factors evaluated as independent predictors of 3 month adverse outcome (defined as modified Rankin scale ≥3 or death) were assessed using multiple logistic regression analysis. The variables included in the model were CHA2DS2-VASc score, cardiovascular risk factors, reperfusion therapy and severity of stroke on admission according to NIHSS score.

The sites and sizes of the qualifying infarcts showed at CT scan were determined based on standard templates as follows: (1) small, when a lesion was ≤1.5 cm in the anterior or posterior circulation, (2) medium, when a lesion was in a cortical superficial branch of middle cerebral artery [MCA], in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery [PCA], in the PCA
branch or in a cortical superficial branch of the anterior cerebral artery [ACA]), (3) large anterior, when a lesion involved the complete territory of ACM, ACP, or ACA, in 2 cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than 1 artery territory [eg, MCA associated to ACA territories]), (4) large posterior, when a lesion was ≥1.5 cm in the brain stem or cerebellum.

A possible correlation between lesion size and CHA2DS2-VASc score was investigated for using a $\chi^2$-squared ($p$ for trend).

**Results:**

Overall, 1,029 consecutive patients were included in the study (mean age 77.2 ± 9.5 years; 560 females and 469 males). The distribution of CHA2DS2-VASc score in the study patients is reported in the Table 1.

Nine patients were excluded from the analysis as their NIHSS score was not available. Of the 1,020 patients included in the analysis, 606 patients had an admission NIHSS score lower and 414 patients higher than 10. The mean NIHSS score for each of the CHA2DS2-VASc scores are reported in the Table 1 ($p=0.071$). A linear correlation was found between severity of stroke and CHA2DS2-VASc score ($r^2 0.010$, $p=0.001$) (fig. 1). On multivariate analysis, CHA2DS2-VASc score correlated with the severity of stroke (OR $1.084$, 95% CI 1.003-1.172, $p=0.041$, for each one point increase). Considering the modest correlation, a logistic regression with a ROC graph procedure, to get the $c$ statistic, was performed and it evidenced that the area under the curve was 0.60 (0.56-0.63), $p=0.0001$ for severe stroke.

When factors included in the CHA2DS2-VASc score were assessed individually for a correlation between stroke severity, only increasing age and female sex resulted being significantly correlated to stroke severity according to NIHSS ($p=0.007$ and $p =0.001$, respectively) (Table 2).

A correlation was also found between pre-stroke CHA2DS2-VASc score and lesion size. After excluding patients treated with revascularization, 70% of patients with CHA2DS2-
VASc score of 8 or 9 had a medium-large lesion, while 70% of patients with CHA2DS2-VASc score of 0 had a small lesion (Figure 2, p for trend=0.042).

At 90-days, 1.019 patients were available for the functional outcome analysis (10 patients were lost at follow-up). The correlation between pre-stroke CHA2DS2-VASc score and 90 day outcome is reported in Table 1.

On multivariate analysis, both NIHSS score on admission and CHA2DS2-VASc score were correlated with disability and mortality at 90 days (mRS≥3) (OR 1.236, 95% CI 1.197-1.277, p<0.0001; OR 1.278; 95% CI 1.100-1.484, p=0.001 respectively for each one point increase).

The administration of thrombolytic therapy and the use of statins at admission resulted being independently correlated with better outcome (OR 0.313, 95% CI 0.204-0.481, p<0.0001; OR 0.585, 95% CI 0.354-0.967, p=0.036; respectively).

**Discussion:**

The results of our study found correlations between pre-stroke CHA2DS2-VASc score and severity of stroke at presentation, according to NIHSS, as well as between CHA2DS2-VASc score and 90-day mortality and disability, as measured by mRS.

Therein, indicating that a higher CHA2DS2-VASc score is predictive of a worse outcome.

Moreover, in post-hoc analyses we also found, first, a correlation between higher CHA2DS2-VASc score and greater lesion size. This finding could support previous studies that have reported an association between CHA2DS2-VASc score and major vessel occlusion in patients with acute ischemic stroke and AF. Second, our study results also is in line with past studies reporting that among risk factors, age and female sex are more predictive of severe stroke.

A strength of this study was that several stroke assessment scores were prospectively utilized, and each of these scores were correlated to the CHA2DS2-VASc score. Whereas, several past studies were retrospective and used only a single assessment score.
In conclusion, we found an increasing CHA2DS2-VASc score in AF patients predicted a more severe stroke at presentation, leading to a higher rate of disability and mortality at 90 days. This result highlights the need for physicians to more regularly investigate for AF in patients with other known vascular risk factors, especially increasing age and female sex.
**Table 1:** Stroke severity (NIHSS) and 90 day outcome according to pre-stroke CHA2DS2-VASc score

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Pre-stroke CHA2DS2-VASc (n=1029)</th>
<th>NIHSS at admission (mean)^</th>
<th>90-day mRS score≥3* (n=1019***)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>17 (1.7%)</td>
<td>5.18 ± 5.75</td>
<td>4/17 (23.5%)</td>
</tr>
<tr>
<td>1</td>
<td>54 (5.2%)</td>
<td>8.30 ± 8.16</td>
<td>16/53 (30.2%)</td>
</tr>
<tr>
<td>2</td>
<td>91 (8.9%)</td>
<td>8.31 ± 6.70</td>
<td>34/90 (37.7%)</td>
</tr>
<tr>
<td>3</td>
<td>200 (19.4%)</td>
<td>8.86 ± 7.10</td>
<td>81/198 (40.9%)</td>
</tr>
<tr>
<td>4</td>
<td>243 (23.6%)</td>
<td>9.12 ± 7.22</td>
<td>125/242 (51.6%)</td>
</tr>
<tr>
<td>5</td>
<td>206 (20.0%)</td>
<td>9.67 ± 7.73</td>
<td>113/202 (55.9%)</td>
</tr>
<tr>
<td>6</td>
<td>129 (12.8%)</td>
<td>9.70 ± 6.50</td>
<td>78/129 (60.5%)</td>
</tr>
<tr>
<td>7</td>
<td>66 (6.4%)</td>
<td>10.30 ± 8.20</td>
<td>43/65 (66.1%)</td>
</tr>
<tr>
<td>8-9</td>
<td>23 (2.2%)</td>
<td>12.09 ± 6.68</td>
<td>16/23 (69.6%)</td>
</tr>
</tbody>
</table>

\(^p\) for trend=0.071

*\(p\) for trend=0.0001

** Nine patients were excluded from the analysis as their NIHSS score was not available

***1019 patients were available for the final functional outcome analysis (10 patients were lost at follow-up)

**Table 2.** Multivariate analysis for correlation of stroke severity and any of each component of CHA2DS2-VASC score.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (for each year increase)</strong></td>
<td>1.020</td>
<td>0.007</td>
<td>1.005-1035</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>0.367</td>
<td>0.001</td>
<td>0.515-0.175</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1.172</td>
<td>0.296</td>
<td>0.870-1.575</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0.759</td>
<td>0.110</td>
<td>0.542-1.065</td>
</tr>
<tr>
<td><strong>Stroke/TIA/Thromboembolism</strong></td>
<td>0.972</td>
<td>0.849</td>
<td>0.723-1.306</td>
</tr>
<tr>
<td>History</td>
<td>NIHSS</td>
<td>CHADS2</td>
<td>VASC</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-------</td>
<td>--------</td>
<td>-------</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>1.049</td>
<td>0.777</td>
<td>0.753-1.462</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1.034</td>
<td>0.832</td>
<td>0.760-1.406</td>
</tr>
</tbody>
</table>

Fig. 1. Linear correlation between NIHSS at admission and CHA2DS2-VASC score.
**Figure 2:** CHA$_2$DS$_2$-VASC score and lesion size (excluding patients treated with revascularization).

![Graph showing CHA$_2$DS$_2$-VASC score and lesion size](image)

* $p$ for trend = 0.042

**Disclosures**

On behalf of all authors, the corresponding author states that there is no conflict of interest.

M. Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer and Pfizer. G. Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. C. Becattini received honoraria as a member of the speaker bureau of Bristol Meyer Squibb and Bayer. P. Michel received Research Grant by Swiss National Science Foundation and Swiss Heart Foundation; he received speaker fees by Bayer, Boehringer Ingelheim, Covidien, St. Jude Medical; he received honoraria as advisory relationship by Pierre-Fabre, Bayer, Bristol Meyer Squibb, Amgen, and Boehringer Ingelheim. J. Putaala received honoraria for lectures related to atrial fibrillation and anticoagulants for Orion Pharma, Bristol Meyer Squibb, Pfizer,
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