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ORIGINAL ARTICLE

Predictive role of CHADS₂ and CHA₂DS₂-VASc scores on stroke and thromboembolism in patients without atrial fibrillation: a meta-analysis

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ABSTRACT

Objective: CHA₂DS₂-VASc is the extension of the CHADS₂ score developed by Birmingham 2009. This risk stratification schema is often used in clinical setting when considering additional risk factors for developing stroke in AF patients. However, its role in the non-AF population is unknown. This study was designed to evaluate the accuracy of the CHADS₂ and the CHA₂DS₂-VASc scoring systems.

Methods: Studies designed for CHADS₂ and CHA₂DS₂-VASc score in stratifying the risks for stroke development in non-AF patients were included.

Results: Among the 114 studies identified, six trials were chosen finally and included for meta-analysis. The pooled diagnostic odds ratio (DOR) for CHADS₂ and CHA₂DS₂-VASc was 2.86 (95% CI = 1.83–4.28) and 2.80 (95% CI = 1.83–4.28), respectively. CHA₂DS₂-VASc score was of better sensitivity than CHADS₂ score (0.920 vs. 0.768). However, both scores were showed to have inherent heterogeneity and poor specificity.

Conclusions: Though having good diagnostic accuracy, the clinical application of the CHADS₂ and CHA₂DS₂-VASc scores in predicting risk of stroke development in non-AF patients still needs further validation.

KEY MESSAGE

- The overall diagnostic accuracy of CHADS₂ and CHA₂DS₂-VASc in stroke-risk stratification was good in patients with non-atrial fibrillation.

Introduction

According to a recent update from the American Heart Association, the age-adjusted death rate for stroke as an underlying cause of death was 37.9 per 100,000 (1). The prominent risk factors for stroke include high blood pressure, diabetes mellitus, atrial fibrillation, high blood cholesterol, etc. Atrial fibrillation (AF) alone increases the risk of stroke by five-fold throughout all ages (2) and the risk substantially underestimated as AF is often asymptomatic and mostly undetected clinically (3). There has been great interest in developing stroke-risk prediction schemes for identifying patients at high risk of stroke, such as AF (4). CHADS₂ (Congestive heart failure, hypertension, age ≥75 years, diabetes, prior stroke/transient ischemic attack (TIA; double score)) and CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75 years (double score), diabetes, prior stroke or TIA (double score), vascular disease, age 65–74 years, sex class (female)) scoring systems have gained prominent status as key prediction tools for stroke-risk stratification in AF (5,6). In both systems, patient stratification falls under three risk categories, 0 score is low risk, 1 is intermediate and ≥2 is high risk (7).

Reports indicate that both CHADS₂ and CHA₂DS₂-VASc can predict thromboembolic events after supraventricular arrhythmia (8). However, the CHADS₂ scheme has many limitations, including classification of a large proportion of patients as being at intermediate risk and does not include many stroke-risk factors (9,10).
But, the CHA2DS2-VASc extends the stroke-risk factors of CHADS2 to include vascular diseases, age 65–74 years, and sex class, females. The CHA2DS2-VASc scheme has been shown to be as good as (and possibly better than) the CHADS2 scheme in predicting high-risk patients with AF who develop stroke and thromboembolism (4,11). Chen et al. suggested that though the clinical utility of the CHADS2 and CHA2DS2-VASc scores are similar in predicting stroke and thromboembolism (TE), CHA2DS2-VASc has an advantage of identifying extremely low-risk patients with AF (12). Studies elsewhere also suggest that CHA2DS2-VASc is often best to identify patients at ‘truly low risk’ of stroke/TE (13,14). It has also been shown to be effective in identifying patients at lower risk of poor outcomes and serious cardiac complications within three months following ischemic stroke, irrespective of the presence or absence of AF (15).

Lip et al. have suggested that stroke-risk stratification schema used for AF can also be applied to non-AF populations with a similar (modest) predictive value. Owing to their simplicity, CHADS2 scores could potentially be used for a ‘quick’ evaluation of stroke risk in non-AF populations, in a similar manner to AF populations (4). Recent reports provide further evidence for the clinical utility of CHADS2 and CHA2DS2-VASc scores in stroke-risk stratification (16–18). CHADS2 also had been shown to have an impact on all-cause mortality after stroke, regardless of whether patients had AF (19,20). In fact, the CHADS2 score, which was originally developed for AF has been shown to have even greater prognostic value in patients who do not have AF (19).

While meta-analysis and systematic reviews on the diagnostic accuracy of CHADS2 and CHA2DS2-VASc scores in patients with AF are available (7,12), systematic reviews on the accuracy of CHADS2 and CHA2DS2-VASc in non-AF population is lacking. The present study was undertaken to evaluate the accuracy of the CHADS2 and the CHA2DS2-VASc scoring systems in stratifying the stroke risk of patients with non-AF.

Methods
Selection criteria
We performed a literature search of the PubMed, Central, and EMBASE databases from inception until January 8, 2015, using a combination of the terms “CHADS2 OR CHA2DS2-VASc score AND stroke AND predict OR sensitivity OR specificity; and CHADS2 OR CHA2DS2-VASc AND stroke NOT atrial fibrillation”. Only studies in patients without AF, where the incidence of stroke or any other thromboembolic event was predicted using CHADS2, CHA2DS2-VASc scores, or both were included. A quantitative outcome was necessary for inclusion and the primary endpoints were defined as stroke or thromboembolic events.

We excluded letters, comments, editorials, case reports, proceedings, personal communications, as well as studies with no quantitative outcome. We also excluded trials where the study population was primarily patients with AF, or cannot distinguish patients without AF from the whole population included.

Study selection and data extraction
Studies identified by the search strategy were hand-selected and data extracted by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted. The information like, the first author, year of publication, and the journal, study design, number of participants, participants’ age and gender, follow-up time, incidence of prior stroke, and the outcome measures were extracted.

The outcome measures analyzed were the endpoint events, like a stroke or any thromboembolic events, or hospitalization for stroke or transient ischemia.

Data analysis
Diagnostic odds ratio (DOR) was used as the index of diagnostic performance of CHADS2 and CHA2DS2-VASc scores in predicting stroke. DOR is defined as the ratio of odds of being tested positive in those who have a disease to the odds of being tested positive in those who do not have a disease; and therefore it is a single index that summarizes statistics for the accuracy of a diagnostic test (i.e., sensitivity and specificity). DOR >1 indicates good diagnostic performance in distinguishing stroke. Summary receiver operating characteristic (SROC) was also plotted for the overall testing accuracy. Larger area under SROC curve, ranging from 0.5 to 1.0, indicates good diagnostic performance. The pooled estimate of DOR was calculated by DerSimonian and Laird random-effects model and a two-sided p value <0.05 was considered statistically significant. Heterogeneity was assessed by using the Cochran Q and the I2 statistic. For the Q statistic, p < 0.10 was considered statistically significant for heterogeneity. The I2 statistic indicates the percentage of the observed between-study variability due to heterogeneity. The suggested ranges are as follows: no heterogeneity (I2 = 0–25%), moderate heterogeneity (I2 = 25–50%), large heterogeneity (I2 = 50–75%), and extreme heterogeneity (I2 = 75–100%). All statistical
analyses were performed using the statistical software Meta-Disc 1.4 (XI Cochrane Colloquium, Barcelona, Spain) and Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

**Quality assessment**

The quality of included studies was assessed according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) (21). Data extraction and quality assessment were carried out independently by the same two investigators, and disagreements were resolved by consensus.

**Results**

**Literature search**

Of the 114 studies identified through the database, 80 studies were excluded due to lack of relevancy. After assessing 31 articles for full text reviewing, we excluded 25 studies, for reasons like, only patients with AF (n = 8), patients cannot be distinguished from the whole population (n = 8), no reported CHADS2 or CHA2DS2-VASc scores (n = 2), incomplete data to calculate DOR (n = 3), and comments or duplicate studies (n = 4). Six studies were included in the final meta-analysis. The flow diagram of the selection of trials is shown in Figure 1.

**Study characteristics**

The basic characteristics of the six studies included in this meta-analysis are summarized in Table 1. All of them provided information about the CHADS2 score and four of them provided CHA2DS2-VASc score. Except for one small study (8) (n = 108), five studies recruited at least 800 study participants (4,18,19,22,23). The mean or median age of study participants ranged from 54.8 to 72.5 years. The proportion of males ranged from 47% to 80.72%. Three large cohort studies followed participants for up to 19 years. The proportion of stroke history ranged from 2.6% to 15.7% (Table 1).

**Meta-analysis**

In five of the included studies, the cut-off point for CHADS2 score was 1, and a CHADS2 score equal to or greater than 1 was defined as positive results, otherwise it was defined as negative. The cut-off point was set to 2 for the other one study (Morillas et al.), as there were no participants having CHADS2 score of 0 (22). Four of the six individual studies showed significantly better diagnostic performance of CHADS2 score in predicting stroke (DOR =1.93–5.00). The pooled DOR summarized by DerSimonian and Laird random-effects model was 2.86 (95% CI = 1.79–4.55) with large heterogeneity across studies (Cochran-Q = 16.78, p = 0.0049, I2 = 70.2%) (Figure 2(A)). The SROC illustrated that the area under the curve was 0.6728 (standard error [SE] = 0.0609) (Figure 2(B)). The pooled sensitivity was 0.768 (95% CI = 0.731–0.803) and the pooled specificity was 0.420 (95% CI = 0.410–0.429; data not shown).

There was no evidence of heterogeneity between four individual studies (Cochran-Q = 0.10, p = 0.9918, I2 = 0%). The pooled DOR was 2.80 (95% CI = 1.83–4.28), indicating good test accuracy of CHA2DS2-VASc score (Figure 3(A)). The area under SROC was 0.6655 (SE = 0.0326) (Figure 3(B)). The pooled sensitivity and specificity was 0.920 (95% CI = 0.884–0.948) and 0.159 (95% CI = 0.151–0.167), respectively (data not shown).

![Figure 1. Flow diagram of study selection.](image-url)
Table 1. Summary of the basic characteristics of selected studies for meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Age, years (mean ± SD)</th>
<th>Male (%)</th>
<th>Follow-up time (range)</th>
<th>Prior stroke (%)</th>
<th>Endpoint events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morillas et al. (2015)</td>
<td>Prospective</td>
<td>887</td>
<td>72.5 ± 5.7</td>
<td>47%</td>
<td>Median 804 days</td>
<td>7%</td>
<td>Hospitalization for stroke/TIA</td>
</tr>
<tr>
<td>Champion et al. (2014)</td>
<td>Prospective</td>
<td>108</td>
<td>No ATE: 64 (40; 80)*</td>
<td>56%</td>
<td>15 months</td>
<td>15.7%</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Biancari et al. (2013)</td>
<td>Retrospective</td>
<td>1226</td>
<td>64.0 ± 0.27</td>
<td>74%</td>
<td>7.2 ± 4.5 year</td>
<td>6.8%</td>
<td>Stroke in 30 days</td>
</tr>
<tr>
<td>Lip et al. (2013)</td>
<td>Cohort study</td>
<td>3524</td>
<td>54.8 ± 12.3</td>
<td>47%</td>
<td>Median 15.9 years</td>
<td>2.6%</td>
<td>Stroke</td>
</tr>
<tr>
<td>Hornero et al. (2012)</td>
<td>Retrospective cohort</td>
<td>2910</td>
<td>64.7 ± 9.741</td>
<td>80.72%</td>
<td>19 year</td>
<td>6.43%</td>
<td>Stroke</td>
</tr>
<tr>
<td>Poci et al. (2012)</td>
<td>Cohort study</td>
<td>1890</td>
<td>64 ± 10</td>
<td>70%</td>
<td>10 year</td>
<td>3.2%</td>
<td>Stroke</td>
</tr>
</tbody>
</table>

*Data were presented by median and 10%–90% percentiles.
Abbreviations: ATE: arterial thromboembolic events; TIA: transient ischemic attack.

Figure 2. Meta-analysis for the diagnostic performance of CHADS2 in predicting stroke. (A) Forest plot; (B) summary receiver operating curve.
The pooled estimate for the test accuracy of CHADS$_2$ score was stable as depicted by the leave-one-out sensitivity analysis; the magnitude and direction of DOR did not change considerably when any one individual study was removed (Figure 4(A)). However, for CHA$_2$DS$_2$-VASc score, the study by Lip et al. (4) had slight influence on the pooled DOR (Figure 4(B)).

**Quality assessment**

The quality assessment analysis of the studies included is shown in Table 2. The selection bias and performance bias were relatively low in all the studies. However, all patients were not included in the final analysis of two studies, and it was unclear in one of the studies, indicating attrition bias. Similarly, there was high concern regarding the applicability of the studies included.

**Discussion**

The present meta-analysis assessed the clinical utility of CHADS$_2$ and CHA$_2$DS$_2$-VASc scoring system for predicting stroke and other thromboembolic events in
patients with non-AF. The validity of CHADS2 and CHA2DS2-VASc scores on stroke-risk stratification in patients with AF has been well documented (5–8,12,24,25). However, the application of CHADS2 and CHA2DS2-VASc schema in patients with non-AF is relatively new and a few studies have explored this relatively simple method of risk assessment in non-AF population (4,17,19,22). The current review is the first to systematically analyze the existing literature and to evaluate the accuracy of the CHADS2 and the CHA2DS2-VASc in stroke-risk stratification in patients with non-AF.

The results reveal that the pooled DOR and SROC for both scoring systems were relatively close (DOR: CHADS2 2.86, CHA2DS2-VASc 2.80; SROC: CHADS2 0.6728, CHA2DS2-VASc 0.6655), suggesting that both CHADS2 and CHA2DS2-VASc were equally reliable and accurate in predicting stroke and other thromboembolic events in patients with non-AF (Figures 2 and 3). CHA2DS2-VASc score showed better sensitivity, as compared to CHADS2 (0.920 vs. 0.768; Figure 4). However, the specificity of both scores was not so good, with CHA2DS2-VASc score worse than the CHADS2 (0.159 vs. 0.420), which is probably because the risk factor profile of non-AF patients is not similar to that of AF patients and therefore, it is necessary that the risk factors for scoring schemes must be modified accordingly.

The studies included in the current meta-analysis comprised of a wider patient population, in terms of race and ethnicity, etiology of stroke/thromboembolism, risk profiles, treatment care and setting, use of anticoagulants, follow-up times, and primary endpoints. Two of the studies were retrospective analysis (18,23), while the rest were either prospective (8,19,22) or registry-based with prospective follow-up (4). However, all of them except for Biancari et al. (18), did not consider the subtype of stroke (ischemic or hemorrhagic) while analyzing their results. The presence of these confounding factors may account for the heterogeneity observed in the current analysis. Nevertheless, the overall results reveal the diagnostic accuracy of CHADS2 and the CHA2DS2-VASc in non-AF patients as well, as demonstrated previously for the AF patient population (7,12,13).

In a cohort study comprising of patient population with and without AF, Poci et al. have demonstrated that CHADS2 scores had even greater prognostic value in non-AF patients than in the AF patients, for whom it was originally developed for (19). Further, they have also shown that the 10-year all-cause mortality was also strongly associated with the CHADS2 score in

![Figure 4. Sensitivity-analysis for the diagnostic performance of (A) CHADS2 and (B) CHA2DS2-VASc.](image-url)
Table 2. Quality assessment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias (low/high/unclear)</th>
<th>Reference standard</th>
<th>Flow and timing</th>
<th>Patient selection</th>
<th>Index test</th>
<th>Reference index test</th>
<th>Index test results interpreted correctly</th>
<th>Was there a threshold value of the index test to define a target condition?</th>
<th>Was the index test condition appropriate for the patient population?</th>
<th>Was there an appropriate sample size of patients included in the study?</th>
<th>Was there a consecutive or random sample of patients included in the study?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morillas et al. (2015)</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Unclear</td>
<td>Low/unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
</tr>
<tr>
<td>Champion et al. (2014)</td>
<td>Unclear</td>
<td>Low/unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
</tr>
<tr>
<td>Biancari et al. (2013)</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High/unclear</td>
<td>Low/unclear</td>
<td>High/unclear</td>
</tr>
<tr>
<td>Hornero et al. (2012)</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Low/unclear</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

Hornero and colleagues have compared CHADS$_2$ and the CHA$_2$DS$_2$-VASc scoring systems with other predictive models for surgical coronary artery bypass grafting (CABG) stroke in patients undergoing isolated CABG and have found that CHADS$_2$ and the CHA$_2$DS$_2$-VASc have good accuracy in predicting perioperative post-CABG stroke similar to other more complicated models of risk assessment (23). Biancari et al. assessed the risk of stroke at later periods after CABG (18). Through a systematic follow-up of patients post-surgery, they have found that freedom from stroke at 30 days, and at 1-, 5-, and 10-year follow-ups were 97.5%, 96.8%, 92% and 87%, respectively, and CHADS$_2$ and the CHA$_2$DS$_2$-VASc were able to predict both immediate and late strokes as well as any fatal strokes (c-statistics: CHADS$_2$, 0.641 and CHA$_2$DS$_2$-VASc, 0.716). Our pooled diagnostic ratio further validates these individual study results, where CHADS$_2$ and the CHA$_2$DS$_2$-VASc scoring was shown to identify patients of high risk of stroke and can be used as a quick evaluation tool for stroke risk in both AF and non-AF populations, as suggested by Lip et al. (4).

There are other comparable studies that explored the diagnostic accuracy of CHADS$_2$ and CHA$_2$DS$_2$-VASc in this patient population (15–17), however we did not include them because of incomplete data reporting. Similarly, our present analysis did not assess the role of stroke in increased mortality, as none of the studies included reported the distribution of patient deaths at each level of CHADS$_2$ and CHA$_2$DS$_2$-VASc scores. The utility of pre-stroke CHADS$_2$ and CHA$_2$DS$_2$-VASc scores in predicting long-term outcomes in non-AF patients with acute ischemic stroke has been previously reported (16). Patients in the intermediate (pre-stroke CHADS$_2$ and CHA2DS2-VASc scores $= 1$) and high risk ($\geq 2$) subgroups had a higher 5-year mortality and stroke recurrence. Reports elsewhere also demonstrate the benefit of CHADS$_2$ (26) and CHA$_2$DS$_2$-VASc (27) in predicting in-hospital and short-term mortality rate in patients with AF. Though, it should be noted that this benefit was not observed in pre-stroke-risk assessment. Reports suggest that CHADS$_2$ scoring was not reliable in predicting in-hospital mortality or risk for thrombus formation, especially in patients with low CHADS$_2$ scores (26,28). In a retrospective analysis of 559 cardiac
resynchronization therapy and implantable defibrillator patients, Perini et al., have shown that the risk of hospitalization and death is double for patients whose CHA2DS2-VASc score is >5. However, no such association was observed for the CHADS2 score (29).

There are several limitations to the current analysis. Besides the heterogeneity of the included studies mentioned before, the cut-off points in each study were also varied, thus making it difficult to have a subgroup analysis of different risk levels. One of the main limitations for the application of CHADS2 is that it cannot differentiate between intermediate and low risk level, and patients with a score of 1 or 2 may have a stroke risk close to or even below the threshold for net benefit, thus potentially exposing them to unnecessary risk and burden of anticoagulant therapy (10,30,31). The present review failed to offer any additional evidence for the utility of CHADS2 and CHA2DS2-VASc scores in discriminating patients of low and intermediate risk. Another major limitation to this study is that, we did not have enough individual patient data to do the subgroup analysis to account for the wide range of variations in the patient population. Similarly, most studies did not classify data based on the etiology or the stroke subtypes, nor did they provide data on the therapeutics administered, as anticoagulants and other vitamin K antagonists may affect the stroke outcome. In addition, we combined stroke and thromboembolism as one primary endpoint and the average incidence of different risk stratifications in this meta-analysis may not be the true stroke rate, thus introducing a possible bias. Further, our attempts to conduct meta-analysis on the role of stroke and increased mortality as assessed by CHADS2 and CHA2DS2-VASc scores in this patient population were not successful, due to the lack of mortality data. The distribution of the number of patient deaths at each score level of CHADS2 and CHA2DS2-VASc was not provided by the included studies.

In summary, the current analysis indicates that in patients with non-AF, the overall diagnostic accuracy of CHADS2 and CHA2DS2-VASc in stroke-risk stratification was good. However, due to the heterogeneity of the included studies and the low specificity, the present results need to be further validated in multicentric trials, with a larger cohort of patient population and after adjusting for variations in risk profiles, stroke subtypes and other potential confounding factors.

**Disclosure statement**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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**References**


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