The value of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS\textsubscript{2} score 0–1: A nationwide cohort study

Jonas Bjerring Olesen\textsuperscript{1}; Christian Torp-Pedersen\textsuperscript{1}; Morten Lock Hansen\textsuperscript{1}; Gregory Y. H. Lip\textsuperscript{2}

\textsuperscript{1}Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark; \textsuperscript{2}University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK

Summary

North American and European guidelines on atrial fibrillation (AF) are conflicting regarding the classification of patients at low/intermediate risk of stroke. We aimed to investigate if the CHA\textsubscript{2}DS\textsubscript{2}-VASc score improved risk stratification of AF patients with a CHADS\textsubscript{2} score of 0–1. Using individual-level linkage of nationwide Danish registries 1997–2008, we identified patients discharged with AF having a CHADS\textsubscript{2} score of 0–1 and not treated with vitamin K antagonist or heparin. In patients with a CHADS\textsubscript{2} score of 0, 1, and 0–1, rates of stroke/thromboembolism were determined according to CHA\textsubscript{2}DS\textsubscript{2}-VASc score, and the risk associated with increasing CHA\textsubscript{2}DS\textsubscript{2}-VASc score was estimated in Cox regression models adjusted for year of inclusion and anti-platelet therapy. The value of adding the extra CHA\textsubscript{2}DS\textsubscript{2}-VASc risk factors to the CHADS\textsubscript{2} score was evaluated by c-statistics, Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI). We included 47,576 patients with a CHADS\textsubscript{2} score of 0–1, from these 7,536 (15.8\%) were CHA\textsubscript{2}DS\textsubscript{2}-VASc score=0, 10,062 (21.2\%) were CHA\textsubscript{2}DS\textsubscript{2}-VASc score=1, 14,188 (29.8\%) were CHA\textsubscript{2}DS\textsubscript{2}-VASc score=2, 14,188 (29.8\%) were CHA\textsubscript{2}DS\textsubscript{2}-VASc score=3, and 1,480 (3.1\%) were CHA\textsubscript{2}DS\textsubscript{2}-VASc score=4. Of the cohort with a CHADS\textsubscript{2} score of 0–1, the stroke/thromboembolism rate per 100 person-years increased with increasing CHA\textsubscript{2}DS\textsubscript{2}-VASc score (95\% confidence interval): 0.84 (0.65–1.08), 1.79 (1.53–2.09), 3.67 (3.34–4.03), 5.75 (5.33–6.21), and 8.18 (6.68–10.02) at one year follow-up with CHA\textsubscript{2}DS\textsubscript{2}-VASc scores of 0, 1, 2, 3, and 4, respectively. Patients with a CHADS\textsubscript{2} score=0 were not all ‘low risk’, with one-year event rates ranging from 0.84 (CHA\textsubscript{2}DS\textsubscript{2}-VASc score=0) to 3.2 (CHA\textsubscript{2}DS\textsubscript{2}-VASc score=3). Results from Cox regression analyses, NRI, and IDI confirmed the improved predictive ability of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score in the AF patients who have a CHADS\textsubscript{2} score of 0–1. In conclusion, the CHA\textsubscript{2}DS\textsubscript{2}-VASc provides critical information on risk of stroke in AF patients with a CHADS\textsubscript{2} score of 0–1 that can aid a decision of using anti-coagulation. Even in patients categorised as ‘low risk’ using a CHADS\textsubscript{2} score=0, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score significantly improved the predictive value of the CHADS\textsubscript{2} score alone and a CHA\textsubscript{2}DS\textsubscript{2}-VASc score=0 could clearly identify ‘truly low risk’ subjects. Use of the CHA\textsubscript{2}DS\textsubscript{2}-VASc score would significantly improve classification of AF patients at low and intermediate risk of stroke, compared to the commonly used CHADS\textsubscript{2} score.

Keywords

Atrial fibrillation, epidemiology, stroke, risk score

Introduction

The risk of stroke in patients with atrial fibrillation (AF) is not homogeneous and is dependent upon the presence or absence of various stroke risk factors (1, 2). These stroke risk factors have been used to formulate stroke risk stratification schemes that have – until recently – artificially divided patients into low, moderate, and high risk categories (3–5) even though stroke risk is a continuum.

The CHADS\textsubscript{2} score (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke [double weight]) is one such stroke risk stratification scheme, derived from the amalgamation of the AF Investigators and SPAF (Stroke Prevention in AF) stroke risk schemes, and validated in a large administrative dataset (6). In older guidelines, the CHADS\textsubscript{2} score has been used as the basis of treatment recommendations (3), whereby a score of ≥2 indicates ‘high risk’ and oral anticoagulation (e.g. warfarin) is recommended, whilst a score =1 indicates ‘intermediate risk’ and ‘warfarin or aspirin’ is recommended; and a score=0 indices ‘low risk’ and aspirin is recommended.

Whilst simple the CHADS\textsubscript{2} score has many limitations which have been debated (7, 8), especially by the non-inclusion of many common stroke risk factors. Indeed, recent evidence suggests that
The CHADS2 and CHA2DS2-VASc scores

All patients had their CHADS2 and CHA2DS2-VASc scores calculated at baseline (6, 25), for exact diagnoses and drug codes see Olesen et al. (14, 24). The CHADS2 score is the sum of one point each for the presence of heart failure, hypertension, age ≥75 years, and diabetes, and two points for previous stroke/thromboembolism (6). The CHA2DS2-VASc score is the sum of one point each for the presence of heart failure, hypertension, diabetes, vascular disease, age 65–74 years, and female gender, and two points each for the presence of previous stroke/thromboembolism and age ≥75 years (13).

Outcome

The outcome under investigation was hospitalisation or death from stroke/thromboembolism, i.e. including peripheral artery embolism, transient ischaemic attack, and ischaemic stroke (ICD-10: G458, G459, I63, I64, I74) (13, 14, 26). During follow-up, patients were censored if they died from other causes than stroke/thromboembolism.
Table 1: Baseline characteristics for atrial fibrillation patients with CHADS$_2$ score 0–1.

<table>
<thead>
<tr>
<th></th>
<th>Total n=47,576</th>
<th>CHADS$_2$ score = 0 n=19,444</th>
<th>CHADS$_2$ score = 1 n=28,132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>69.4 (14.7)</td>
<td>58.8 (11.9)</td>
<td>76.8 (11.6)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>949 (2.0)</td>
<td>0</td>
<td>949 (3.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8,081 (17.0)</td>
<td>0</td>
<td>8,081 (28.7)</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>18,183 (38.2)</td>
<td>0</td>
<td>18,183 (64.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>919 (1.9)</td>
<td>0</td>
<td>919 (3.3)</td>
</tr>
<tr>
<td>Stroke (previous)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>5,791 (12.2)</td>
<td>1,592 (8.2)</td>
<td>4,199 (14.9)</td>
</tr>
<tr>
<td>Age 65–74 years</td>
<td>13,043 (27.4)</td>
<td>7,526 (38.7)</td>
<td>5,517 (19.6)</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>22,017 (46.3)</td>
<td>7,258 (37.3)</td>
<td>14,759 (52.5)</td>
</tr>
<tr>
<td>Antiplatelet treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>12,259 (25.8)</td>
<td>3,322 (17.1)</td>
<td>8,937 (31.8)</td>
</tr>
<tr>
<td>Clopidogrel or persantine</td>
<td>1,372 (2.9)</td>
<td>332 (1.7)</td>
<td>1,040 (3.7)</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7,536 (15.8)</td>
<td>7,536 (38.8)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10,062 (21.2)</td>
<td>7,739 (39.8)</td>
<td>2,323 (8.3)</td>
</tr>
<tr>
<td>2</td>
<td>14,310 (30.1)</td>
<td>3,870 (19.9)</td>
<td>10,440 (37.1)</td>
</tr>
<tr>
<td>3</td>
<td>14,188 (29.8)</td>
<td>299 (1.5)</td>
<td>13,889 (49.4)</td>
</tr>
<tr>
<td>4</td>
<td>1,480 (3.1)</td>
<td>0</td>
<td>1,480 (5.3)</td>
</tr>
</tbody>
</table>

CHADS$_2$ and CHA$_2$DS$_2$-VASc: see text

Figure 1: Selection of study population.
Statistical analysis

For all analyses we examined two periods of maximum follow-up, i.e. one year and 12 years follow-up. Event rates of stroke/thromboembolism per 100 person-years were calculated according to CHADS2 and CHA2DS2-VASc score, and Kaplan-Meier estimates of probability of remaining free of stroke/thromboembolism according to CHA2DS2-VASc score were used for illustrating event rates until one year follow-up. Cox proportional-hazard analyses adjusted for year of inclusion and antiplatelet treatment were constructed to investigate the risk associated with increasing CHA2DS2-VASc score in patients with CHADS2 score 0, 1, and 0–1, respectively. Compared to the CHADS2 score, we evaluated if inclusion of the CHA2DS2-VASc score added significant information to the Cox regression models using c-statistics (Harrell’s C) (27) and likelihood ratio tests. Also, the value of adding the extra covariates from the CHA2DS2-VASc score was evaluated by Net Reclassification Improvement (IDI), as described by Pencina et al. (28). NRI quantifies correct movement (NRI) and Integrated Discrimination Improvement (IDI), as described by Pencina et al. (28). NRI quantifies correct movement (NRI) and Integrated Discrimination Improvement (IDI), as described by Pencina et al. (28). IDI investigate differences between integrated sensitivity and specificity for models with and without the extra CHA2DS2-VASc covariates (28). We applied the one year of follow-up results for the NRI and IDI calculation since these are not based on survival statistics.

A two-sided p-value <0.05 was considered statistically significant. All analyses were performed with SAS statistical software version 9.2 (SAS Institute Inc., Cary, NC, USA) and Stata statistical software version 11.0 (StataCorp LP, College Station, TX, USA).

Ethics

No ethical approval is required for retrospective register studies in Denmark. The study was approved by The Danish Data Protection Agency (No. 2008–41–2685).

Results

Of our cohort, 47,576 subjects had a CHADS2 score of 0–1, from which 19,444 (40.9%) had a CHADS2 score=0 and 28,132 (59.1%) had a CHADS2 score=1 (Fig. 1). Event rates for stroke and thromboembolism per 100 person-years in non-warfarin treated patients are shown in Table 2, Kaplan-Meier estimates of probability of remaining free of stroke/thromboembolism according to CHA2DS2-VASc score in patients with CHADS2 score 0–1 are illustrated in Figure 2, and results from Cox regression analyses are illustrated in Figure 3.

The stroke/thromboembolic event rate for CHADS2 score=0 was 1.59 per 100 person-years at one-year follow-up, and 1.28 per 100 person-years at 12-year follow-up. Even amongst patients categorised as a CHADS2 score=0, there was a graded increase in the stroke/thromboembolic rate; ranged from 0.84 to 3.2 per 100 person-years at one-year follow-up when subdivided by CHA2DS2-VASc scores (Table 2 and Fig. 2). A CHA2DS2-VASc score=0 identified a truly low risk cohort, with annual event rates at one- and 12-year follow-up of 0.84 and 0.76, respectively, per 100 person-years.

Table 2: Event rate of stroke/thromboembolism per 100 person-years in atrial fibrillation patients.

<table>
<thead>
<tr>
<th>CHADS2 score</th>
<th>1 year follow-up</th>
<th>12 years follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years</td>
<td>Events</td>
</tr>
<tr>
<td>CHADS2 score 0–1</td>
<td>40,272</td>
<td>1,405</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 0</td>
<td>6,919</td>
<td>58</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>8,880</td>
<td>159</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 2</td>
<td>11,863</td>
<td>435</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 3</td>
<td>11,473</td>
<td>660</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 4</td>
<td>1,137</td>
<td>93</td>
</tr>
<tr>
<td>CHADS2 score 0</td>
<td>17,327</td>
<td>275</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 0</td>
<td>6,919</td>
<td>58</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>6,811</td>
<td>119</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 2</td>
<td>3,347</td>
<td>90</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 3</td>
<td>250</td>
<td>8</td>
</tr>
<tr>
<td>CHADS2 score 1</td>
<td>22,945</td>
<td>1,130</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 1</td>
<td>2,069</td>
<td>40</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 2</td>
<td>8,516</td>
<td>345</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 3</td>
<td>11,223</td>
<td>652</td>
</tr>
<tr>
<td>CHA2DS2-VASc = 4</td>
<td>1,137</td>
<td>93</td>
</tr>
</tbody>
</table>

CHADS2 and CHA2DS2-VASc see text
In patients with a CHADS$_2$ score=1 or score 0–1, a similar gradation in stroke/thromboembolic event rates was seen when these patients were subdivided into CHA$_2$DS$_2$-VASc scores of 1, 2, 3 and 4. The patients with a CHADS$_2$ score=1 had stroke event rates that ranged from 1.93 to 8.18 per 100 person-years, when subdivided by CHA$_2$DS$_2$-VASc scores (Table 2 and Fig. 2).

Using CHA$_2$DS$_2$-VASc score=0 as the reference in Cox regression models, at one-year follow-up the hazard ratios associated with CHA$_2$DS$_2$-VASc scores 1, 2, 3, and 4 were 2.10, 4.20, 6.52, and 9.10, respectively (Fig. 3).

In patients with CHADS$_2$ score 0–1, c-statistics of the Cox regression model were significantly improved from 0.632 (95% confidence interval 0.619–0.646) to 0.663 (0.650–0.676) when the CHA$_2$DS$_2$-VASc score was used for stroke risk categorisation instead of the CHADS$_2$ score. In patients with a CHADS$_2$ score=0, c-statistics of the Cox regression model adjusted for year of inclusion and antiplatelet therapy were 0.573 (0.539–0.608) and, 0.641 (0.610–0.671) when the CHA$_2$DS$_2$-VASc score was included. Similar in patients with a CHADS$_2$ score=1, the c-statistics improved from 0.527 (0.510–0.544) to 0.581 (0.565–0.597) by the inclusion.
of the CHA2DS2-VASc score. The likelihood ratio test investigating if the additional risk factors included in CHA2DS2-VASc improved the predictive value of the Cox regression analysis compared to CHADS2 was highly significant in all risk strata (p<0.001), and the smallest improvement in −2log likelihood was 48.3 (seen for one-year follow-up in CHADS2 score=0 patients); indicating strong performance of the CHA2DS2-VASc score.

At one-year follow-up and using the CHA2DS2-VASc score, 1,307/1,405 (93.0%) patients with a stroke/thromboembolic event were reclassified to a higher risk category (increased risk score), while 36,410/46,171 (78.9%) patients without event were reclassified to an increased score; NRI=14.2% and p<0.001. For events, CHA2DS2-VASc increased the risk score by mean 1.60 (standard deviation 0.72) while the score for non-events were increased by 1.23 (0.82). Adding the CHA2DS2-VASc score in patients with CHADS2 score 0–1, IDI was 0.003 and the area under the receiver–operator characteristic curve (AUC) was improved by 0.042 (p<0.001).

Discussion

In this study, we have shown that even in patients categorised as ‘low risk’ using a CHADS2 score=0, the CHA2DS2-VASc score can further refine stroke risk stratification. Indeed, a CHA2DS2-VASc score=0 could clearly identify ‘truly low risk’ subjects, whilst those defined using a CHADS2 score=0 are not low risk, with one-year event rates ranging from 0.84 (CHA2DS2-VASc score=0) to 3.2 (CHA2DS2-VASc score=3). Furthermore, in patients categorised as CHADS2 score=0, 1, or 0–1, respectively, the additional risk factors included in CHA2DS2-VASc significantly improved the predictive value of the Cox regression analysis compared to CHADS2 score alone.

The major clinical implications of this work are that use of the CHA2DS2-VASc score would significantly improve classification of AF patients at low and intermediate risk of stroke, compared to the commonly used CHADS2 score. Since the latter is the basis of some guidelines that only recommend aspirin or no therapy for patients at low stroke risk (3, 17, 18), and even prescribing standards (19), this may lead to many AF patients being provided suboptimal thromboprophylaxis and being at substantial risk of stroke, which has a high mortality and disability when due to AF (29).

This large ‘real world’ study is consistent with the increasing literature from multiple different cohorts that the CHA2DS2-VASc score is better than CHADS2 score in identifying ‘truly low risk’ patients who do not need any antithrombotic therapy (11, 14, 24, 30). A recent Spanish study found that the CHA2DS2-VASc risk stratification schema was better in discriminating between patients at a low and intermediate risk of thromboembolic complications when compared to 2006 ACC/AHA/ESC (American College of Cardiology / American Heart Association / European Society of Cardiology) guideline, 8th edition ACCP guideline, and Framingham schemes (31). Also, the CHA2DS2-VASc score even seems to refine stroke risk assessment in ‘low-risk’ AF patients after ablation (32).

The present analysis represents the largest ‘real world’ cohort study of non-warfarin treated AF patients with a CHADS2 score=0–1. Indeed, stroke prediction should be assessed in non-warfarin treated patients, whilst potential harm (i.e. bleeding from treatment with warfarin) should be assessed in an ‘on treatment’ population on warfarin. Recently, Taillandier et al. (33) reported a small cohort of 616 AF patients with a CHA2DS2-VASc score=0 from a real-life study, these patients had a low risk of stroke/thromboembolism that was not significantly different between those taking oral anticoagulation, antiplatelet therapy, or no antithrombotic therapy, thus supporting the 2010 ESC guideline recommendations for no antithrombotic therapy in these ‘truly low-risk’ patients (34).

Also, we have previously reported a net clinical benefit analysis, balancing ischaemic stroke against intracranial haemorrhage,

![Figure 3: Risk of stroke/thromboembolism. Results from Cox regression analyses adjusted for year of inclusion and antiplatelet treatment.](image-url)
What is known about this topic?
- North American and European guidelines on atrial fibrillation (AF) are conflicting regarding the classification of patients at low/intermediate risk of stroke.
- Those with CHADS2 score=0 are often described as ‘low risk’.

What does this paper add?
- Patients with a CHADS2 score=0 were not all ‘low risk’, with 1-year event rates ranging from 0.84 (CHA2DS2-VASc score=0) to 3.2 (CHA2DS2-VASc score=3).
- The CHA2DS2-VASc score improved stroke risk reduction in the AF patients who have a CHADS2 score of 0–1.
- Even in patients categorised as ‘low risk’ using a CHADS2 score=0, the CHA2DS2-VASc score significantly improved the predictive value of the CHADS2 score alone and a CHA2DS2-VASc score=0 could clearly identify ‘truly low risk’ subjects.
- Use of the CHA2DS2-VASc score would significantly improve classification of AF patients at low and intermediate risk of stroke, compared to the commonly used CHADS2 score.

The new oral anticoagulant drugs, whether oral direct thrombin inhibitors (e.g. dabigatran) or oral factor Xa inhibitors (e.g. rivaroxaban, apixaban) have changed our approach to thromboprophylaxis. Given the benefits of efficacy and safety, one Markov decision analysis model balancing the relative hazard of ischaemic stroke against the relative hazard of intracranial haemorrhage concluded that the threshold for treatment with a new anticoagulant (using the data for dabigatran in the model) was an annual stroke rate of 0.9%, while the threshold for warfarin was 1.7% (35). This change in the ‘tipping point’ for oral anticoagulation is consistent with a recent modelling analysis by Banerjee et al. (36) which suggests that the net clinical benefit would support use of these new oral anticoagulant drugs at CHA2DS2-VASc score=0.

The CHA2DS2-VASc score improved stroke risk reduction in the AF patients who have a CHADS2 score of 0–1. Of note, aspirin did not have any positive net clinical benefit at any CHADS2 or CHA2DS2-VASc score strata.

Conclusion
This 'real world' nationwide Danish cohort study of patients with NVAF clearly shows that even in patients categorised as 'low risk' using a CHADS2 score=0, the CHA2DS2-VASc score can improve stroke risk stratification. Importantly, a CHADS2 score=0 is not necessarily 'low risk' with stroke rates within the group ranging between 0.84 to 3.2 per 100 person-years, when subdivided by CHA2DS2-VASc scores. In contrast, a CHA2DS2-VASc score=0 could clearly identify 'truly low risk' subjects; one-year follow-up stroke rate of 0.84 per 100 person-years. Use of the CHA2DS2-VASc score would significantly improve classification of AF patients at low and intermediate risk of stroke, compared to the commonly used CHADS2 score.

Conflicts of interest
None of the authors have any conflict of interest to declare directly relevant to this paper. Dr. Olesen has received travel grants from AstraZeneca and Boehringer Ingelheim, and received funding for research from the Lundbeck Foundation. Prof. Torp-Pedersen has served as a consultant for Sanofi Aventis, Cardiome, and Merck, and received travel grants from BMS/Pfizer. Prof. Lip has served as a consultant for Bayer, Astellas, Merck, AstraZeneca, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis.

References
(Writing Committee to Revise the 2001 guidelines for the management of patients with atrial fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. European 2006; 8: 651–745.


