Ischemic Stroke Risk in Patients With Atrial Fibrillation and CHA\textsubscript{2}DS\textsubscript{2}-VASc Score of 1
Systematic Review and Meta-Analysis

Raed A. Joundi, MD, DPhil*; Lauren E. Cipriano, PhD*; Luciano A. Sposato, MD, MBA; Gustavo Saposnik, MD, MSc, FRCP; on behalf of the Stroke Outcomes Research Working Group†

Background and Purpose—The CHA\textsubscript{2}DS\textsubscript{2}-VASc score aims to improve risk stratification of ischemic stroke among patients with atrial fibrillation to identify those who can safely forego oral anticoagulation. Oral anticoagulation treatment guidelines remain uncertain for CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1. We conducted a systematic review and meta-analysis of the risk of ischemic stroke for patients with atrial fibrillation and CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0, 1, or 2 not treated with oral anticoagulation.

Methods—We searched MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science from the start of the database up until April 15, 2015. We included studies that stratified the risk of ischemic stroke by CHA\textsubscript{2}DS\textsubscript{2}-VASc score for patients with nonvalvular atrial fibrillation. We estimated the summary annual rate of ischemic stroke using random effects meta-analyses and compared the estimated stroke rates with published net-benefit thresholds for initiating anticoagulants.

Results—1,162 abstracts were retrieved, of which 10 met all inclusion criteria for the study. There was substantial heterogeneity among studies. The summary estimate for the annual risk of ischemic stroke was 1.61% (95% confidence interval 0.9%–2.27%) for CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1, meeting the theoretical threshold for using novel oral anticoagulants (0.9%), but below the threshold for warfarin (1.7%). The summary incident risk of ischemic stroke was 0.68% (95% confidence interval 0.12%–1.23%) for CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0 and 2.49% (95% confidence interval 1.16%–3.83%) for CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 2.

Conclusions—Our meta-analysis of ischemic stroke risk in atrial fibrillation patients suggests that those with CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 1 may be considered for a novel oral anticoagulant, but because of high heterogeneity, the decision should be based on individual patient characteristics. (Stroke. 2016;47:1364-1367. DOI: 10.1161/STROKEAHA.115.012609.)

Key Words: atrial fibrillation ■ CHA\textsubscript{2}DS\textsubscript{2}-VASc ■ ischemic stroke ■ meta-analysis ■ stroke
therapy, aspirin, or OAC may be the appropriate treatment strategy for some in this class.6

Eckman et al used a Markov state-transition model to estimate the threshold annual risk of ischemic stroke for the use of OAC.7 This tipping point, above which the benefits of OAC in ischemic stroke reduction begin to outweigh the increased risk of bleeding, was found to be an annual ischemic stroke risk of 1.7% for warfarin and 0.9% for dabigatran. We sought to help resolve the uncertainty about OAC treatment with a CHA2DS2-VASc score of 1 by conducting a systematic review and meta-analysis of the annual rate of ischemic stroke in this population and comparing it to the theoretical thresholds for treatment. We also considered patient cohorts with CHA2DS2-VASc scores of 0 and 2 to confirm that our results are concordant with current guideline recommendations.

Methods

Search Strategy and Selection Criteria

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.7 We searched MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science Core Collection from the start of the database up until April 15, 2015. We used multiple permutations of the search term CHA2DS2-VASc to identify all possible articles using the CHA2DS2-VASc score. Search terms are shown in Table I in the online-only Data Supplement. R.A. Joundi and T. Rastgardani reviewed the abstracts for relevance, and no disagreements occurred. Titles and abstracts were screened for our inclusion criteria: mention of nonvalvular AF and CHA2DS2-VASc and stroke. Articles were excluded if the study exclusively recruited patients with a specific comorbidity besides AF, such as diabetes mellitus or postoperative, so that studies included in the meta-analysis would be most representative of the general population and not skewed toward a cohort based on a single disease (e.g., studies only including patients with heart failure or patients with diabetes mellitus). Articles were also excluded if primary data were not available/analyzed (e.g., reviews, editorials, or letters to the editor) or if ischemic stroke was not a measured outcome. Articles had to have event rate for at least 1 stratum of the CHA2DS2-VASc score between 0 and 2 or the necessary data to produce event rate (events and patient-years). Finally, we removed studies not including groups without anticoagulation and duplicate cohorts. For the relevant cohorts within each study, we extracted the available baseline characteristics and the outcome information. If one of patient-years, events, or event rate was missing, we calculated it based on the other 2 values.

We used inverse variance weights to produce summary estimates of the ischemic stroke rate stratified by CHA2DS2-VASc score. For ischemic stroke rates, we calculated variance using 2 methods: (1) variance of a Poisson rate parameter where variance=count of events/person-years of observation)7 and (2) adjusted Wald interval for a proportion proposed by Agresti and Coull8 where the variance of a proportion is computed using an adjusted estimate for the proportion of (events+2)/(person-years of observation+4). For cohorts of patients in which no ischemic strokes were observed, we calculated the variance of the Poisson rate parameter assuming 0.5 observed ischemic strokes; the method of Agresti and Coull needs no adjustment to calculate the variance for studies with zero event observations.

We used random effects analyses because of the heterogeneity across studies in regards to study populations, in particular the proportion of patients on antiplatelet therapy or the proportion of patients with comorbidities, such as hypertension. We quantitatively evaluated the presence of between-study heterogeneity with the Chi-squared test (considered significant if $P<0.1$) and $I^2$, which is independent of the number of studies. For random effects models, we estimated between-study variance using the iterative method of Paule and Mandel.10 A sensitivity analysis was conducted in which the study with the highest stroke rate in each group was removed to ascertain its effect on the summary statistic.

Results

Overall, 1162 manuscripts satisfied the search criteria, 104 were selected on abstract screening based on our inclusion and exclusion criteria, and 44 manuscripts contained the desired information. Among them, 20 articles used ischemic stroke as an outcome. After removing overlapping cohorts and articles without nonanticoagulation groups, 10 articles were included in the analysis (Figure 1). Baseline characteristics of patients are included in Table II in the online-only Data Supplement; substantial variation existed across studies for mean age, comorbidities, and antithrombotic use.

The summary annual risk of ischemic stroke for CHA2DS2-VASc score of 1 was 1.61% (2517 events per 166017 patient-years, 95% confidence interval [CI] 0.3–3.23%; Figure 2). The risk of ischemic stroke for CHA2DS2-VASc score of 0 was 0.68% (761 events per 109,197 patient-years, 95% CI 0.12–1.23%) and for CHA2DS2-VASc score of 2 was 2.49% (4319 events per 133,298 patient-years, 95% CI 1.26–3.83%; Figure 3 in the online-only Data Supplement). For CHA2DS2-VASc score of 1, the summary ischemic stroke risk of 1.61% was above the threshold indicated in Eckman et al1 of 0.9% for NOAC but under the threshold of 1.7% for warfarin. In the sensitivity analysis, we removed the study cohort with the highest risk of stroke. This resulted in a summary annual risk of stroke of 0.50% (95% CI 0.12–0.89%), 0.87% (95% CI 0.28–1.46%), and 1.93% (95% CI 1.21–2.60%) for patients with CHA2DS2-VASc of 0, 1, and 2, respectively.

Discussion

Our estimated annual risk of ischemic stroke in AF patients with CHA2DS2-VASc score of 1 based on the summary

![Figure 1. Study search pathway.](http://stroke.ahajournals.org/)

Joundi et al Meta-Analysis of CHA2DS2-VASc Score 1 1365
measure of 7 studies is 1.61% with substantial uncertainty remaining (95% CI 0.9%–3.23%). Additionally, the summary annual risk was 0.68% for CHA₂DS₂-VASc score of 0 and 2.49% for CHA₂DS₂-VASc score of 2. To our knowledge, this is the first meta-analysis specifically addressing the annual ischemic stroke rate by CHA₂DS₂-VASc, and it provides an improved estimate for the risk of ischemic stroke to guide clinical decision-making.

In keeping with the guidelines, our summary measures suggest that patients with a CHA₂DS₂-VASc score of 0 may not benefit from OAC and patients with a CHA₂DS₂-VASc score of 2 should be strongly considered for OAC, including warfarin. Treatment opportunities have expanded with the development of NOACs, which have an improved safety profile and lower risk of intracranial hemorrhage compared with warfarin (0.7% for NOACs versus 1.5% for warfarin). Using the net-benefit thresholds identified by Eckman et al., we found that patients with a CHA₂DS₂-VASc score of 1 (annual rate of 1.61%) may be eligible for a NOAC (threshold of 0.9%), but likely not warfarin (threshold of 1.7%). These findings are consistent with analyses demonstrating net clinical benefit for NOACs, but not warfarin, in patients with CHA₂DS₂-VASc score of 1.

A limitation of our meta-analysis was the heterogeneity between studies, likely resulting from diversity of ethnicities, antiplatelet use, and risk factors. The rate of stroke in CHA₂DS₂-VASc score of 1 depends on the specific risk factor contributing the point, ranging from 0.7% for being female to 1.9% for having age >65. This has implications because those with a known low risk of ischemic stroke (women with a CHA₂DS₂-VASc score of 1) may not expect a positive net-benefit from NOAC treatment. Greater risk stratification among patients with a CHA₂DS₂-VASc score of 1 is likely important to further clarify ischemic stroke risk and the potential benefit of OAC treatment for patients in this category. The level of detail provided in current reports was not sufficient for us to stratify our analysis on this basis. With the current information, the data favor a personalized, rather than rule-based, approach for patients with CHA₂DS₂-VASc score of 1.

In conclusion, based on an average annual ischemic stroke rate of 1.61%, treatment with NOACs may provide patients with a CHA₂DS₂-VASc score of 1 positive clinical net benefit. However, given the high uncertainty because of heterogeneity of risk conferred by specific factors, a final decision will require judgment incorporating the individual patient’s comorbidities, values, and preferences.

Figure 2. Rate of ischemic stroke per 100-patient years for CHA₂DS₂-VASc score of 1.

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Disclosures
L.A. Sposato has received speaker honoraria from Boehringer Ingelheim. The other authors report no conflicts.

References


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SUPPLEMENTAL MATERIAL

Ischemic Stroke Risk in Patients with Atrial Fibrillation and
CHA$_2$DS$_2$-VASc score of 1: Systematic Review and Meta-analysis

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Gustavo Saposnik, MD, MSc, FRCP, FAHA

This supplemental file includes Supplemental Results, 2 figures, and 2 tables.

Supplemental Figure I. Rate of ischemic stroke per 100-patient years for CHA$_2$DS$_2$-VASc score 0 and 2

Supplemental Figure II. Funnel plots and Egger regression tests

Supplemental Table I. Search terms

Supplemental Table II. Baseline characteristics of patients from final selection of papers
Supplemental Results: Bias assessment

We assessed the quality of studies according to the Cochrane handbook\(^1\), and used funnel plots and Egger regression tests to assess publication bias.\(^2\) Egger regression tests were significant and funnel plots showed considerable asymmetry for all the summary measures (Supplemental Figure II). Overall, 6/10 studies had possible selection bias, due to studies enrolling patients all from the same hospital (4/10), only having paroxysmal atrial fibrillation (1/10), only having patients with age >75 (1/10), enrolling patients who were candidates but unsuitable for treatment with anticoagulation (1/10), using mixed studies/methodologies (1/10), not specifying a blanking period after the diagnosis of atrial fibrillation (5/10), and not specifying how atrial fibrillation was diagnosed (2/10). 7/10 studies had possible performance bias as although they defined their study group initially as ‘no anti-coagulation’, they did not specify if any patients took up anti-coagulation throughout the course of the follow-up period. 1 study treated all patients with anti-arrhythmics. 1 study included 25% females in the CHA2DS2-VASc 0 group based on descriptive table. 6/10 studies had possible attrition bias as there was no specific information regarding patient loss to follow-up. 5/10 studies had possible detection bias, due to not explicitly stating how ischemic stroke was defined (4/10), and not mandating imaging as part of the diagnosis for ischemic stroke (1/10). Lastly, funding bias was present in 3/10 studies, and sources of funding were not mentioned in 5/10 studies. In each analysis, one cohort (Huang et al. for CHA2DS2-VASc 0 and 1 and Siu et al. for CHA2DS2-VASc of 2, which included patients from the same registry) was a substantial outlier, possibly due to a Chinese population recruited at exclusively one centre.
**Supplemental Figures**

**Supplemental Figure I.** Rate of ischemic stroke per 100-patient years for CHA$_2$DS$_2$-VASc 0 and 2.

**A:** CHA$_2$DS$_2$-VASc of 0;  **B:** CHA$_2$DS$_2$-VASc of 2.

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A: CHA$_2$DS$_2$-VASc = 0

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Supplemental Figure II. Funnel plots and Egger regression tests for assessment of publication bias
**Supplemental Tables**

**Supplemental Table I**

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(congestive heart failure and hypertension and diabetes and (stroke or transient ischemic attack or TIA) and vascular disease)
## Supplemental Table II. Baseline characteristics of patients in final selection of papers

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</tbody>
</table>

*RO = retrospective observational; RCT = data from randomized controlled trial
Empty cells = data unavailable
Supplemental References


