Should Every Patient With Atrial Fibrillation and a CHA₂DS₂-VASc Score of 1 Be Anticoagulated? A Systematic Review of 37,030 Patients

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Abstract: Patients with atrial fibrillation (AF) are at risk of thromboembolic events. The CHA₂DS₂-VASc (congestive heart failure, hypertension, age 65–74, diabetes, female sex and vascular disease, which all count for 1 point, and previous transient ischemic stroke/stroke or age ≥75 years, which count for two points) score stratifies this risk and consequently indicates whether anticoagulation is required but leaves room for debate regarding patients with a CHA₂DS₂-VASc score of 1, irrespective of sex. A score of 1, irrespective of sex, is derived from varying risk factors and may represent different risks. We systematically searched PubMed from inception to July 31, 2017, for studies describing thromboembolic risk per risk factor of the CHA₂DS₂-VASc score in patients with AF not treated with an anticoagulant. Two independent reviewers selected, appraised, and extracted the data to determine the thromboembolic risk per risk factor. Per study, risk factors were ranked for highest through lowest risk. Five studies were included, comprising 37,030 subjects with a CHA₂DS₂-VASc score of 1. Numerically, the highest event rates were seen in patients without comorbidities, but aged 65–74 years, while event rates in patients with vascular disease tended to be the lowest. Age 65–74 years is associated with the highest risk, hazard ratios ranging from 1.9 (95% confidence interval, 1.7–2.1) to 3.9 (95% confidence interval, 2.3–6.6), while comorbid cardiovascular conditions are associated with lower, but still considerably increased, risks. The thromboembolic risk differed between the risk factors of the CHA₂DS₂-VASc score in patients with AF, with age 65–74 years associated with the highest and most consistent risk. However, all show a significantly and clinically relevant increased thromboembolic risk. Besides the differences between risk factors of the CHA₂DS₂-VASc score, differences within risk factors may also alter stroke risk.

Key Words: thromboembolic risk, stroke risk, oral anticoagulation, CHA₂DS₂-VASc score, atrial fibrillation

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studies describing patients with a CHA₂DS₂-VASc score of 1 because we assessed the individual risk of each risk factor not influenced by female sex. We excluded studies describing subjects with AF due to a reversible cause, case reports, and nonhuman studies. When a study described subjects with and without OAC, only subjects without OAC therapy were included in this analysis. If the use of an OAC was not clearly described, the total study cohort was excluded. The outcome of interest was thromboembolism or ischemic stroke.

Two reviewers (J.N. and T.K.) selected the titles and abstracts of all search results using Covidence, 2017. The full text article was reviewed for all relevant entries. The references of the selected studies were cross-checked for additional relevant studies. Critical appraisal of nonrandomized studies was assessed using the adjusted Newcastle-Ottawa Quality Assessment Scale for cohort studies. This assessment scale was developed to assess the quality of nonrandomized studies by judging studies on patient selection, ascertainment of exposure, comparability, and assessment of outcome. The scale was implemented to fit the current analysis. The exclusion of subjects based on antiplatelet therapy, such as aspirin or clopidogrel, was appraised as lowering the risk of bias. An adequate follow-up duration was defined as at least 5 years because of the low incidence of thromboembolic events. Studies were supposed to show sufficient adequacy of follow-up when the follow-up rate was 95%. The risk of bias was interpreted as low if the total score was 6 or more. In cases of discrepancies regarding the inclusion of a study or the critical appraisal, a third reviewer (J.R.d.G.) was consulted for consensus.

The results of the included studies were evaluated, and the event rate per 100 person-years was extracted or calculated with corresponding 95% confidence intervals (95% CIs). Furthermore, per study, the risk of a thromboembolic event for each risk factor included in the CHA₂DS₂-VASc score was extracted, described by hazard ratios (HRs) or odds ratios. Next, per study, the risk factors were ranked for highest (rank number 1) through lowest (rank number 5) risk of a thromboembolic event.

This systematic review was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (2015).

RESULTS

The search identified 3,244 unique abstracts (Fig. 1). After review of title and abstract, 48 abstracts were selected for full text screening. Additionally, 2 articles were selected after cross-checking of the reference lists. During full text screening, another 40 articles were excluded based on study design, patient population, intervention, completeness of the data, and outcome. Consequently, 8 studies were included. However, based on overlapping cohorts, 3 more studies were excluded (see Critical Appraisal).

Critical Appraisal

The critical appraisal is shown in Table 1. Overall, the studies were appraised as low risk of bias. The risk of bias was mainly influenced by a lack of information about follow-up duration. Of note, 3 studies followed patients during a relatively short period, on average less than 5 years. One study only reported the event rates per risk factor, but not the number of patients per risk factor. Importantly, 4 studies described overlapping Taiwanese cohorts. The study of Chao et al described the most comprehensive cohort and was appraised the highest; therefore, this study was included for the main analyses.

Study Characteristics

All included studies were nationwide cohort studies (Table 2). The number of subjects ranged from 358 to 20,835 per study, yielding a total of 37,030 subjects. Valvular AF was an exclusion criterion in 3 studies. Thromboembolic events were described per study. The study populations contained different ethnicities, with 21,193 (57.2%) of the subjects being of Asian descent.

Patient Characteristics

The mean age ranged between 58.9 and 74 years. Three studies reported the number of patients suffering from each risk factor individually, comprising 22,057 patients. In these studies, subjects most frequently suffered from hypertension (7,420 [33.6%]), while vascular disease was the least frequent risk factor (1,593 [7.2%]). Tables 3 and 4 list the total number of subjects and the number of subjects with a thromboembolic event per risk factor of the CHA₂DS₂-VASc score. Note that age ≥ 75 years and prior stroke/TIA were not included, as these factors account for 2 points, which was beyond the scope of this analysis. This also holds for the risk factor of female sex, as the ESC guidelines states that this risk factor on its own should be considered as a truly low risk. Chao et al found an annual stroke rate of 2.75% for males with a CHA₂DS₂-VASc score of 1, and 2.55% for females. Olesen et al reported a rate...
### Table 1. Critical Appraisal

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Control</th>
<th>Adequacy of Follow-Up</th>
<th>Outcome</th>
<th>Total Score</th>
<th>CHA2DS2-VASc Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung et al11</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>yes</td>
</tr>
<tr>
<td>Chan et al12</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>no</td>
</tr>
<tr>
<td>Chao et al13</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>yes</td>
</tr>
<tr>
<td>Huang et al17</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>3</td>
<td>yes</td>
</tr>
<tr>
<td>Friberg et al14</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>no</td>
</tr>
<tr>
<td>Olesen et al15</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>yes</td>
</tr>
<tr>
<td>Lin et al16</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>yes</td>
</tr>
<tr>
<td>Olesen et al5</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>4</td>
<td>yes</td>
</tr>
</tbody>
</table>

*Representative of the average patient with atrial fibrillation in the western population.
†Study controls for antiplatelet therapy.
‡Follow-up > 5 years.
§Follow-up rate > 95%.

#### DISCUSSION

In the studies reviewed, all risk factors of the CHA2DS2-VASc score are associated with a significantly increased risk of stroke in patients not using OACs. Studies tend to point toward a specific ranking of the risk factors for stroke. Overall, age 65–74 years is consistently associated with the highest risk. On the other side of the spectrum, cardiovascular conditions such as hypertension, vascular disease, and congestive heart failure are associated with a more modest, but still considerable increase of stroke risk, irrespective of sex.

Besides the differences between risk factors of the CHA2DS2-VASc score, differences within risk factors may alter the risk. We found very small CIs concerning the risk attributed to age 65–74 years, which adds even more robustness to the results and underlines the importance and objectiveness of this risk factor. In contrast, it should be realized that the CHA2DS2-VASc score is a point-based score and does not take into account that there may be differences of thromboembolism of 2.01 per 100 person-years for patients with a CHA2DS2-VASc score of 1. Numerically, the highest event rates were seen in the group aged 65 to 74 years without comorbidities, while event rates in the group with vascular disease tended to be the lowest. Event rates ranged between 1.47 (95% CI, 1.01–2.12) per 100 person-years for vascular disease and 3.5 (95% CI, 3.3–3.7) per 100 person-years for age 65–74. All events risk factors resulted in considerable event rates in the diverse studies. The study of Chan et al12 described the lowest event rates overall and even 0 events in a small group of females with vascular disease.

#### CHA2DS2-VASc Score and Thromboembolic Risk

Figure 2 and Table 5 show the calculated HRs of the thromboembolic risk in subjects with a CHA2DS2-VASc score of 1 per risk factor, with the corresponding ranking. Every risk factor of the CHA2DS2-VASc score was associated with significantly increased thromboembolic risks. HRs describing risk factor age 65 to 74 years tended to be the highest, ranging from HR, 2.97 (95% CI, 2.54–3.48) to HR, 3.9 (95% CI, 2.3–6.6). Of note, the study of Lin et al16 calculated the odds ratios per risk factor. Furthermore, they reported the odds ratio for stroke risk for myocardial infarction, coronary disease, and peripheral artery disease separately. Interestingly, only peripheral artery disease was associated with a significant increased odds ratio compared with no risk factor (data not shown).

A vast amount of the included subjects were of Asian descent, as stated above. When stratified for Asian and non-Asian descent, age 65–74 years remained the highest risk factor, as can be appreciated in Table 5.

No significantly additionally increased risk was observed for the following risk factors: vascular disease in the study by Hung et al11 in the age group 50–64 years, but it did increase the risk in patients aged 65–74 (HR, 1.72 95% CI, 1.03–2.85), congestive heart failure in the study by Friberg et al,14 and both hypertension and diabetes mellitus in the study by Olesen et al.15

#### Ranking of the Risk Factors

When the risk factors of each study were ranked for highest through lowest risk, age 65 to 74 years was associated with the highest thromboembolic risk, while hypertension was generally associated with the lowest thromboembolic risk. HRs describing risk factor age 65 to 74 years were seen in the group aged 65 to 74 years without comorbidities, yielding a HR of 5.87 (5.10–6.76). This, however, did not alter our findings. If anything, it more strongly associated age 65 to 74 years with the highest thromboembolic risk.

#### Comparison of the CHA2DS2-VASc Score and Thromboembolic Risk

The CHA2DS2-VASc score was associated with a significantly increased thromboembolic risk in subjects with a CHA2DS2-VASc score of 1. Numerically, the highest event rates were seen in the group aged 65 to 74 years without comorbidities, while event rates in the group with vascular disease tended to be the lowest. Event rates ranged between 1.47 (95% CI, 1.01–2.12) per 100 person-years for vascular disease and 3.5 (95% CI, 3.3–3.7) per 100 person-years for age 65–74. All events risk factors resulted in considerable event rates in the diverse studies. The study of Chan et al12 described the lowest event rates overall and even 0 events in a small group of females with vascular disease.

The CHA2DS2-VASc score was associated with a significantly increased thromboembolic risk in subjects with a CHA2DS2-VASc score of 1. Numerically, the highest event rates were seen in the group aged 65 to 74 years without comorbidities, while event rates in the group with vascular disease tended to be the lowest. Event rates ranged between 1.47 (95% CI, 1.01–2.12) per 100 person-years for vascular disease and 3.5 (95% CI, 3.3–3.7) per 100 person-years for age 65–74. All events risk factors resulted in considerable event rates in the diverse studies. The study of Chan et al12 described the lowest event rates overall and even 0 events in a small group of females with vascular disease.
within risk factors regarding their severity. The lower thromboembolic risks found for hypertension may, for example, be explained by the difference between well-controlled versus uncontrolled hypertension, which cannot be distinguished by the CHA2DS2-VASc score. Further, vascular disease describes a heterogeneous condition, ranging from myocardial infarction or carotid artery stenosis to peripheral artery disease, subsequently resulting in a gradually increased risk. Last, the thromboembolic risk in heart failure may also differ between patients with a reduced ejection fraction and those with a preserved ejection fraction. The CHA2DS2-VASc score does not consider the severity of heart failure symptoms or reduction in ejection fraction, while a gradually increased risk may be expected coherent with the magnitude of the ejection fraction reduction.

### Table 3. Number of Thromboembolic Events per 100 Person-Years per Risk Factor of the CHA2DS2-VASc Score

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country of Inclusion</th>
<th>Inclusion Criteria</th>
<th>Patients with a CHA2DS2-VASc Score of 1 and No OAC</th>
<th>Main Outcome</th>
<th>Study Duration (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al13 2015</td>
<td>Taiwan</td>
<td>Patients with AF, ≥ 20 years old who did not receive treatment with an OAC or an antiplatelet agent.</td>
<td>20,835</td>
<td>Ischemic stroke</td>
<td>Males: 5.2 Females: 5.9</td>
</tr>
<tr>
<td>Huang et al13 2014</td>
<td>China</td>
<td>Patients with nonvalvular AF, ≥ 20 years old who did not receive treatment with an OAC or an antiplatelet agent.</td>
<td>358</td>
<td>Ischemic stroke</td>
<td>10</td>
</tr>
<tr>
<td>Friberg et al14 2012</td>
<td>Sweden</td>
<td>Patients with nonvalvular AF and survival of the first 14 days after index date.</td>
<td>6,770</td>
<td>Thromboembolism</td>
<td>1.4</td>
</tr>
<tr>
<td>Olesen et al15 2012</td>
<td>France</td>
<td>Patients with nonvalvular AF or Aflutter with known treatment status concerning OAC.</td>
<td>864</td>
<td>Thromboembolism or ischemic stroke</td>
<td>10</td>
</tr>
</tbody>
</table>

Data could not be extracted from the other included studies.

CHA2DS2-VASc indicates congestive heart failure, hypertension, age 65–74, diabetes, female sex and vascular disease, which all count for 1 point, and previous transient ischemic stroke/stroke or age ≥ 75 years, which count for two points; OAC, oral anticoagulation.

### Table 4. Number of Thromboembolic Events per 100 Person-Years per Risk Factor of the CHA2DS2-VASc Score

<table>
<thead>
<tr>
<th>Reference</th>
<th>Vascular Disease</th>
<th>Age 65–74</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al13 2015</td>
<td>(male)</td>
<td>787</td>
</tr>
<tr>
<td>Chao et al13 2015</td>
<td>(female)</td>
<td>455</td>
</tr>
<tr>
<td>Olesen et al11 2011</td>
<td>na</td>
<td>1.47 (1.01–2.12)</td>
</tr>
</tbody>
</table>

Data could not be extracted from the other included studies.

CHA2DS2-VASc indicates congestive heart failure, hypertension, age 65–74, diabetes, female sex and vascular disease, which all count for 1 point, and previous transient ischemic stroke/stroke or age ≥ 75 years, which count for two points; OAC, oral anticoagulation.

*Per 100 person-years.*
Furthermore, differences in the employment of stroke definitions may result in different risks. Friberg et al. described that when TIA, pulmonary embolism, systemic embolism, and unspecified stroke were added to the endpoint, the stroke rate increased 44% in patients with a CHA2DS2-VASc score of 1.14 The included studies used thromboembolism and/or (ischemic) stroke as a main outcome; they did not further specify their outcomes. Our results, however, already show a significantly and clinically apparent increased thromboembolic risk, which may be an underestimation, as outlined above. The CHA2DS2-VASc score was found to better predict truly low-risk patients than the Anticoagulation and Risk Factors in AF score in an Asian population.22

Conversely, OAC increases the bleeding risk. This risk can be assessed by the Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile International Normalized Ratios, Elderly and Drugs or Alcohol score and is useful for the management of correctable risk factors.19 Importantly, risk factors of this score overlap with the CHA2DS2-VASc score. A less frequently used score to assess if a patient will do well on VKA is the sex female, age < 60 years, medical history (> 2 comorbidities), treatment (interacting drugs), tobacco use (2 points), race nonwhite (2 points) score.28 This score, however, faces the same issue of overlapping with the risk factors of the CHA2DS2-VASc score.

Finally, patients may value risks and consequences differently. In fact, a survey by Lahaye et al. concluded that patients would rather suffer from 4 major bleedings to prevent 1 ischemic stroke. This underlines the necessity of shared decision-making, particularly in patient cohorts at moderately increased thromboembolic risk.

Limitations

The currently available literature is limited and challenged by a selected population, variety in study designs, and inconsistent definitions of the outcome. The included studies were all large but retrospective in design; this in itself inflicts bias. Furthermore, the studies mainly included patients with a hospital diagnosis of AF, probably selecting patients with a higher comorbidity profile and thus a higher risk of stroke, as argued by Friberg et al.26 Of note, the study of Friberg et al. has been criticized for excluding patients taking OAC during follow-up, inflicting conditional bias on the future. This could have underestimated the thromboembolic risk in these patients. In certain cases, the CHA2DS2-VASc score was retrospectively calculated based on the prescribed medication related to the risk factors. The risk of
### Table 5. Hazard Ratios and Rank Number per Risk Factor of the CHA2DS2-VASc Score in Patients With Atrial Fibrillation and Without Oral Anticoagulation Prescription, per Study

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Hypertension, HR (95% CI)</th>
<th>Vascular Disease, HR (95% CI)</th>
<th>Diabetes Mellitus, HR (95% CI)</th>
<th>Congestive Heart Failure, HR (95% CI)</th>
<th>Age 65–74, HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al</td>
<td>2.06 (1.79–2.37)</td>
<td>1.68 (1.13–2.123)</td>
<td>2.66 (2.01–3.37)</td>
<td>2.86 (1.73–1.97)</td>
<td>3.09 (2.79–3.341)</td>
</tr>
<tr>
<td>Olesen et al</td>
<td>2.66 (1.48–1.977)</td>
<td>1.71 (1.14–1.237)</td>
<td>2.06 (1.13–3.561)</td>
<td>2.98 (1.05–1.03)</td>
<td>3.08 (2.07–3.352)</td>
</tr>
<tr>
<td>Friberg et al</td>
<td>1.19 (1.13–1.286)</td>
<td>1.17 (1.11–1.251)</td>
<td>1.19 (1.06–3.123)</td>
<td>1.36 (1.26–1.48)</td>
<td>2.97 (2.14–3.498)</td>
</tr>
<tr>
<td>Olesen et al</td>
<td>2.19 (1.12–1.392)</td>
<td>1.19 (1.07–2.339)</td>
<td>1.19 (1.08–3.355)</td>
<td>1.14 (1.06–1.256)</td>
<td>2.31 (1.27–1.238)</td>
</tr>
<tr>
<td>Reference</td>
<td>Percent of total ranks</td>
<td>Percent of total ranks</td>
<td>Percent of total ranks</td>
<td>Percent of total ranks</td>
<td>Percent of total ranks</td>
</tr>
</tbody>
</table>

For each study, the determinants were ranked for highest (rank number 1) through lowest (rank number 5) risk of a thromboembolic event. Afterwards an overall ranking was determined.

**REFERENCES**


