Added Predictive Ability of the CHA$_2$DS$_2$VASc Risk Score for Stroke and Death in Patients With Atrial Fibrillation

The Prospective Danish Diet, Cancer, and Health Cohort Study

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**Background**—The objective of this study was to evaluate the added predictive ability of the CHA$_2$DS$_2$VASc prediction rule for stroke and death in a nonanticoagulated population of patients with atrial fibrillation.

**Methods and Results**—We included 1603 nonanticoagulated patients with incident atrial fibrillation from a Danish prospective cohort study of 57 053 middle-aged men and women. The Net Reclassification Improvement was calculated as a measure to estimate any overall improvement in reclassification with the CHA$_2$DS$_2$VASc score as an alternative to the CHADS$_2$ score. After 1-year follow-up, crude incidence rates were 3.4 per 100 person-years for stroke and 13.6 for death. After a mean follow-up of 5.4 years (±3.7 years), the crude incidence rates for stroke and death were 1.9 and 5.6, respectively. During the entire observation period, the c-statistics and negative predictive values were similar for both risk scores. The Net Reclassification Improvement analysis showed that 1 of 10 reclassified atrial fibrillation patients would have been upgraded correctly using the CHA$_2$DS$_2$VASc score.

**Conclusions**—Both the CHADS$_2$ as well as the CHA$_2$DS$_2$VASc risk score can exclude a large proportion of patients from having high risk of stroke or death. However, using the CHA$_2$DS$_2$VASc risk score, fewer patients will fulfill the criterion for low risk (and are truly low risk for thromboembolism). For every 10 extra patients transferred to the treatment group at 5 years, using the CHA$_2$DS$_2$VASc risk score, 1 patient would have had a stroke that might have been avoided with effective treatment. (Circ Cardiovasc Qual Outcomes. 2012;5:00-00.)

**Key Words:** atrial fibrillation ■ stroke ■ CHADS$_2$ ■ CHA$_2$DS$_2$VASc ■ c-statistics ■ AUC ■ Net Reclassification Improvement ■ oral anticoagulation ■ risk score

Atrial fibrillation is the most common cardiac rhythm disorder and is associated with an increased risk of mortality and morbidity from stroke and thromboembolism. An essential part of clinical management of atrial fibrillation involves decision-making on oral anticoagulant therapy or not, given that oral anticoagulant therapy significantly reduces stroke (by 64%) and all-cause mortality (by 26%) compared with placebo or control.

Evidence-based guidelines have largely been based on stroke risk stratification schema derived from randomized trial data, comparing the outcome in specific populations of patients. The well-recognized risk factors for stroke in atrial fibrillation patients are congestive heart failure, hypertension, advanced age, diabetes, and previous stroke. These stroke risk factors have been used to formulate stroke risk stratification schema that have traditionally classified patients into low-, moderate-, and high-risk strata—so that the “high-risk” patients could be targeted for oral anticoagulant therapy with a Vitamin K antagonist (VKA; eg, warfarin), given the disutility and inconvenience associated with this class of drugs for maintaining therapeutic anticoagulation. The artificial division of stroke risk stratification into low-/moderate-/high-risk strata (despite stroke in atrial fibrillation being a continuum of risk) is poorly predictive. In the present study, we regard patients with ≥1 stroke risk factor as high risk.

In the clinical setting, decisions on thromboprophylaxis are based on the estimation of the actual risk in a specific individual patient, and thus, general rules based on specific groups of patients derived from trial datasets (especially since the historic trials randomly assigned <10% of the screened patients) may be difficult to implement. For example, the commonly used CHADS$_2$ score was an amalgamation of the...
(trial cohort based) SPAF-1 and Atrial Fibrillation Investigators stroke risk schemes,3,4 and, despite its many limitations, is still attractive, given its simplicity and accurate validation for everyday clinical practice.6

WHAT IS KNOWN

- The CHADS2 and CHA2DS2VASc scores are risk scoring systems used for stroke risk stratification in atrial fibrillation.
- While simple, the CHADS2 score does not include many common stroke risk factors, and its limitations have been recently highlighted.
- Given that stroke risk in atrial fibrillation is a continuum, a paradigm shift now focuses on better identification of truly low-risk patients who do not need any antithrombotic therapy, whereas those with ≥1 stroke risk factors can be considered for effective stroke prevention therapy, which is essentially oral anticoagulation.

WHAT THE STUDY ADDS

- Using the CHA2DS2VASc risk score, fewer patients will fulfill the criterion for low risk (and are truly at low risk for thromboembolism) and the negative predictive value is increased.
- Our results suggest that for every 10 extra patients transferred to the treatment group at 5 years, using the CHA2DS2VASc risk score, 1 patient would have had a stroke that might have been avoided with effective treatment.

With the availability of new oral anticoagulant drugs that overcome the limitations of VKAs, a paradigm shift has been proposed to be more inclusive (rather than exclusive) of other stroke risk factors in refining stroke and thromboembolism risk stratification for patients with atrial fibrillation.7 A risk factor-based approach with the acronym CHA2DS2VASc has been proposed in recent guidelines,8 in which “truly low-risk” subjects can even be considered for no antithrombotic therapy, whereas in atrial fibrillation patients with ≥1 stroke risk factors oral anticoagulant therapy is recommended or preferred, either with well-managed VKAs or with one of the new agents (eg, dabigatran).

The goal of stroke prediction models is to guide clinicians and patients toward the most appropriate antithrombotic strategy. Various measures have been proposed to describe discrimination in diagnostic tests. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve, also referred to as the c-statistic, has been the most popular method to evaluate or compare the performance of the previous risk score CHADS2 with the CHA2DS2VASc risk score.5,7-9 For example, one Danish nationwide cohort study showed that the CHA2DS2VASc score had a superior performance in terms of c-statistics or AUC than the CHADS2 score in predicting patients at high risk, at 1, 5, and 10 years of follow-up.10 The CHA2DS2VASc score has consistently been more successful than the CHADS2 score in identifying those who are truly at low risk for thromboembolism, with a high negative predictive value (NPV).10-12 NPV is defined as the proportion of subjects with a negative test (CHADS2 or CHA2DS2VASc with a score of zero) that did not develop an event during follow-up. In 2008, Pencina et al13 proposed another method of comparing risk prediction rules, which was applied in the Framingham Heart Study. They proposed assessing classification using Net Reclassification Improvement (NRI), which focuses on reclassification tables constructed separately for participants with and without events and quantifies the accurate movement between risk categories. Thus, if the new scoring system (or prediction rule) is better, the proportion of scored patients moving upward (positive sign) for events and downward (negative sign) for nonevents should be higher than the proportion moving in the opposite direction.

To evaluate the added predictive ability of the CHA2DS2VASc prediction rule for stroke in a nonanticoagulated population of patients with atrial fibrillation, we analyzed data from a Danish prospective epidemiological cohort study of 57,053 middle-aged men and women and compared the predictive value of the CHADS2 and CHA2DS2VASc scores in cases of incident atrial fibrillation. We hypothesized that the CHA2DS2VASc score that also included vascular disease, female sex, and age 65 to 74 years on top of the CHADS2 score would be superior to the CHADS2 score in identifying a “truly low-risk” patient among patients with incident atrial fibrillation. The scoring and classification abilities of the prediction rules were evaluated and compared in terms of the AUC, NPV, and NRI.

Methods

The Diet, Cancer, and Health Study

For this study, we used the Diet, Cancer, and Health cohort, established in 1993 to 1997. The study design has been reported in detail elsewhere.14 The primary objective of this prospective study was to investigate the etiologic role of diet and lifestyle in the development of cancer, and 57,053 participants were enrolled (27,178 men and 29,876 women, respectively). The study participants were aged between 50 and 64 years, living in the urban areas of Copenhagen and Aarhus, and without a cancer diagnosis registered in the Danish Cancer Registry at baseline. Participants were, for this study, followed from 1995 until December 2009.

The Danish Diet, Cancer, and Health cohort has detailed information on demographics, existing comorbidities, and individual risk factors, including the stroke risk factors from the CHADS2 and CHA2DS2VASc risk schemes. Cross-linkage between the Danish Diet, Cancer, and Health cohort, the National Registry of Patients and the Danish prescription registry, provides detailed information on incident atrial fibrillation, stroke, and death and specific information about censoring from emigration and death during follow-up until December 2009. The study was conducted in accordance with the Helsinki Declaration II and approved by the regional ethics committees.

Case Finding

The Danish Diet, Cancer, and Health cohort subjects were linked to the National Registry of Patients, dating back to 1976, using the Danish Personal Identification number. This is a unique and national identification number that is part of the personal information stored in the Civil Registration System. The study population in the present study included participants who developed incident atrial fibrillation during follow-up. Codes from the International Classification of Diseases, 10th Revision, were used to identify patients with incident atrial fibrillation. The study population was compared with the initial study population. The study population had a higher frequency of men and a lower frequency of women and patients with diabetes and stroke. The study population was also younger than the initial study population, with a lower frequency of patients aged ≥75 years.

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CHADS2, we compared stroke and death as primary and secondary

stroke identified from the National Registry of Patients.

available from the Civil Registration System and ICD-codes for

outcomes, respectively. Information on emigration or death is

Diabetes; MI, myocardial infarction; and PAD, peripheral arterial disease.

and 90 percentiles for continuous covariates. The CHADS2 and

analysis with proportions for discrete covariates and medians with 10

diagnosis) for the stroke risk factors (Table 1), we used descriptive

To describe the distribution at baseline (ie, time of atrial fibrillation

Statistical Methods

The covariates included in the CHADS2 and CHA2DS2VASc pre-

dictions were identified using the corresponding ICD codes presented in online-only Data Supplement Table I.

Clinical Characteristic*  Median (p10; p90)% (N)

No. of participants 1603

Age, y, at time of atrial fibrillation 66.6 (59.1; 74.3)

Age ≥75 y 8.0 (128)

Age 65–74 y 52.8 (647)

Women 39.6 (636)

Follow-up time, y 5.4 (0.9; 11.0)

Medical history at time of atrial fibrillation

Congestive heart failure

Heart failure 13.5 (217)

Left ventricular dysfunction 10.9 (175)

Hypertension 28.7 (460)

Diabetes 9.9 (158)

Stroke/TIA/TE

Vascular disease (prior MI, PAD, or aortic plaque) 1

Age 65–74 y 1

Sex category (female) 1

TIA indicates transient ischemic attack; LV, left ventricular; TE, thromboem-

bolism; MI, myocardial infarction; and PAD, peripheral arterial disease.

Diseases (ICD) were used to extract admissions for atrial fibrillation. ICD-8 was used until 1994, and hereafter ICD-10 was used. Atrial fibrillation and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), whereas in ICD-10, atrial fibrillation and atrial flutter have one ICD code (148). Therefore, atrial flutter cases have also been included in the present study. The study population was defined as incident cases of atrial fibrillation after recruitment who had not emigrated before diagnosis with atrial fibrillation. Cases diagnosed simultaneously with stroke, thromboembolism, and transient ischemic attack or patients who died on the same day they were diagnosed with atrial fibrillation were excluded for analysis. Based on the Danish prescription registry, all atrial fibrillation patients having had prescriptions of anticoagulant agents, warfarin, or phen-

procoumon (ATC code B01A) within 360 days to the outcome event or end of follow-up were excluded.

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Cohort Outcome Assessment

For testing the hypothesis of CHA2DS2VASc superiority to CHADS2, we compared stroke and death as primary and secondary outcomes, respectively. Information on emigration or death is available from the Civil Registration System and ICD-codes for stroke identified from the National Registry of Patients.

Cohort Exposure Assessment

The covariates included in the CHADS2 and CHA2DS2VASc prediction rules were identified using the corresponding ICD codes presented in online-only Data Supplement Table I.

Statistical Methods

To describe the distribution at baseline (ie, time of atrial fibrillation diagnosis) for the stroke risk factors (Table 1), we used descriptive analysis with proportions for discrete covariates and medians with 10 and 90 percentiles for continuous covariates. The CHADS2 and CHA2DS2VASc risk scores used are presented in Table 1.

The incidence rates (per 100 person-years) were calculated for each level of both CHADS2 and CHA2DS2VASc to compare how well the scoring systems detected atrial fibrillation patients with a low risk of stroke. Furthermore, the probability value for trend was calculated to investigate whether the risk of stroke or death was higher according to higher score values. Analyses were done at 1-year follow-up and for the entire period of follow-up.

Time-dependent ROC curves were used for further comparison of the risk scoring systems. The area under the ROC curve (AUC) represents the probability that a random person with an event has a higher risk score than a random person without an event. In addition, we calculated the time-dependent NPV for both scores, using zero as cutoff value.

The NRI described by Pencina et al13 was used to compare the individual level changes in risk assessment for the 2 scoring systems, in which CHA2DS2VASc is considered as a refinement of CHADS2. The divergences of risk assessment are summarized by evaluating the proportions of patients with a correct/incorrect change in-risk in the groups of patients ending up as cases (NRIcase) and as noncases (NRINoncase). NRIcase + NRINoncase = P(correct reclassification group) minus P(incorrect reclassification group). Positive NRI means overweight of correct reclassified subjects, and negative NRI means overweight of incorrect reclassified subjects. To account for varying follow-up time, the time-dependent approach of Champles and Gui16 was used, and we report NRIcase and NRINoncase as suggested by Pepe17 as well as the weighted NRI case (NRIweight). Because the CHA2DS2VASc score cannot reduce the risk classification compared with the CHADS2 score, the quantity NRIweight/NRIweight (noncase) expresses the expected number of additional treated patients per reclassified case-patient.

Bootstrap confidence intervals were calculated using 100 bootstrap samples. Data were analyzed using Stata version 12 (Stata Corporation, College Station, TX).

Results

From this cohort, we identified 3325 patients with atrial fibrillation who met the inclusion criteria. In these patients, 117 atrial fibrillation diagnoses were given on the day of a stroke diagnosis; 3 had been diagnosed with thromboembolism on the day of admission; 31 were excluded because of transient ischemic attack, and 4 were excluded from analysis because they died on the day of admission. Using the Danish prescription registry, 1567 patients were classified as receiving treatment with warfarin or phenprocoumon and therefore were excluded from further analysis. Thus, our study population consisted of 1603 nontreated patients with incident atrial fibrillation (967 male, 636 female, presented in Table 2). The numbers in each score value in the CHADS2 and CHA2DS2VASc scores are presented in Table 3.

After 1-year follow-up, crude incidence rates were 3.4 per 100 person-years for stroke and 13.6 for death. After a mean follow-up of 5.4 years (±3.7 years), the crude incidence rates

<table>
<thead>
<tr>
<th>Clinical Characteristic*</th>
<th>Whole Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, at time of atrial fibrillation</td>
<td>66.6 (59.1; 74.3)</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>8.0 (128)</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>52.8 (647)</td>
</tr>
<tr>
<td>Women</td>
<td>39.6 (636)</td>
</tr>
<tr>
<td>Follow-up time, y</td>
<td>5.4 (0.9; 11.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical history at time of atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Left ventricular dysfunction</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
</tr>
<tr>
<td>Age 65–74 y</td>
</tr>
<tr>
<td>Sex category (female)</td>
</tr>
</tbody>
</table>

*At time of atrial fibrillation.
for stroke and death were 1.9 and 5.6 per 100 person-years, respectively. Thus, the incidence of stroke and death was relatively higher after a short period of time after atrial fibrillation than after a longer period of follow-up. Incidence rates for stroke and death are presented in Tables 4 and 5, respectively. Incidence rates for stroke and death increases according to the risk scores and the risk estimates shows that after 1-year follow-up (per 100) per year, for the highest score using CHADS2 (score = 5) was 48.6 (12.1;190) and for CHA2DS2VASc (score = 7), 48.4 (12.1;190). Higher scores in both scoring systems were associated with higher risks of stroke or death from scores ≥2 and for death only during full follow-up from score ≥1, compared with score = 0. These higher scores include only few patients and have very wide confidence intervals (CI).

Time-dependent area under the ROC curves for the 2 scoring systems were similar with fully overlapping confidence intervals (Figures 1 and 2). Both scoring systems had for both end points an almost constant AUC level. At 5-year follow-up, the statistics for stroke were CHADS2 AUC: 0.64 (95% CI, 0.56; 0.71) and CHA2DS2VASc AUC: 0.66 (95% CI, 0.59; 0.72). The corresponding statistics for death were CHADS2 AUC: 0.62 (95% CI, 0.59; 0.66) and CHA2DS2VASc AUC: 0.63 (95% CI, 0.59; 0.67) (full data not shown). The NPV for CHA2DS2VASc, using zero as cutoff value, had a trend to be superior in predicting stroke or death compared with the CHADS2 score, but this was not considered different, as indicated by the overlapping confidence intervals (Figures 3 and 4). For both systems and end points, the NPV decreased over time. At 5-year follow-up, the statistics for stroke were CHADS2 NPV: 0.93 (95% CI, 0.91; 0.95) and CHA2DS2VASc NPV: 0.95 (95% CI, 0.91; 0.98). The corresponding statistics for death were CHADS2 NPV: 0.82 (95% CI, 0.79; 0.84) and CHA2DS2VASc NPV: 0.85 (95% CI, 0.80; 0.89) (full data not shown).

Comparing the CHADS2 and CHA2DS2VASc risk scores using NRI at 1-year follow-up for the patient with reported stroke, the systems disagreed for 10 patients of 107, corresponding to 9% being a crude estimate of the NRIcases statistics. The time-dependent estimates of the reclassification indexes for stroke (Figure 5) showed that NRIcases increased over time and remained positive. At 1-year follow-up, the NRIcases equaled 17% (95% CI, 9%-26%) and 31% (95% CI, 28%-34%), respectively (full data not shown). For noncases, the levels were fairly constant and negative with approximately -39% (95% CI, -41%: -38%) for stroke and -41% (95% CI, -43%: -40%) for death (full data not shown).

The reclassification analysis for stroke yielded a weighted NRI of -3% (95% CI, -6%: 1%) after 5 years of follow-up by using the CHA2DS2VASc score instead of the CHADS2 score. This means that in a setting where the case and noncase

Table 3. Distribution of Risk Scores in the Study Population

<table>
<thead>
<tr>
<th>Score value</th>
<th>CHADS2, % (n)</th>
<th>CHA2DS2VASc, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>54.7 (877)</td>
<td>16.0 (257)</td>
</tr>
<tr>
<td>1</td>
<td>25.6 (411)</td>
<td>28.0 (449)</td>
</tr>
<tr>
<td>2</td>
<td>12.2 (196)</td>
<td>26.3 (422)</td>
</tr>
<tr>
<td>3</td>
<td>5.0 (80)</td>
<td>16.0 (256)</td>
</tr>
<tr>
<td>4</td>
<td>2.0 (32)</td>
<td>7.6 (122)</td>
</tr>
<tr>
<td>5</td>
<td>0.4 (6)</td>
<td>4.2 (67)</td>
</tr>
<tr>
<td>6</td>
<td>0.1 (1)</td>
<td>1.4 (22)</td>
</tr>
<tr>
<td>7</td>
<td>...</td>
<td>0.4 (6)</td>
</tr>
<tr>
<td>8</td>
<td>...</td>
<td>0.1 (1)</td>
</tr>
<tr>
<td>9</td>
<td>...</td>
<td>0.1 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (1603)</td>
<td>100 (1603)</td>
</tr>
</tbody>
</table>

*At time of atrial fibrillation.

Table 4. Incidence Rates for Stroke by CHADS2 and CHA2DS2VASc Scores in the Study Population

<table>
<thead>
<tr>
<th>Score value</th>
<th>CHADS2 1-Year Follow-Up</th>
<th>CHADS2 Full Follow-Up</th>
<th>CHA2DS2VASc 1-Year Follow-Up</th>
<th>CHA2DS2VASc Full Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9 (1.2; 3.1)/15</td>
<td>1.2 (0.9; 1.6)/55</td>
<td>0.9 (0.2; 3.4)/2</td>
<td>0.9 (0.5; 1.4)/14</td>
</tr>
<tr>
<td>1</td>
<td>2.3 (1.2; 4.6)/8</td>
<td>2.2 (1.6; 3.1)/32</td>
<td>2.2 (1.2; 4.3)/9</td>
<td>1.1 (0.8; 1.7)/25</td>
</tr>
<tr>
<td>2</td>
<td>8.9 (5.3; 15.0)/14</td>
<td>4.1 (2.7; 6.3)/22</td>
<td>2.2 (1.1; 4.3)/8</td>
<td>2.4 (1.8; 3.3)/39</td>
</tr>
<tr>
<td>3</td>
<td>7.9 (3.3; 19.1)/5</td>
<td>4.0 (2.1; 7.8)/9</td>
<td>6.3 (3.7; 10.9)/13</td>
<td>3.4 (2.3; 5.1)/24</td>
</tr>
<tr>
<td>4</td>
<td>28.5 (12.3; 70.9)/5</td>
<td>19.5 (10.1; 37.5)/9</td>
<td>7.8 (3.9; 15.6)/8</td>
<td>4.2 (2.5; 7.2)/14</td>
</tr>
<tr>
<td>5</td>
<td>0.0</td>
<td>11.5 (1.6; 82.0)/1</td>
<td>8.4 (3.1; 22.5)/4</td>
<td>3.8 (1.7; 8.4)/6</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
<td>0.0</td>
<td>31.3 (10.1; 97.1)/3</td>
<td>23.1 (9.6; 55.5)/5</td>
</tr>
<tr>
<td>7</td>
<td>...</td>
<td>...</td>
<td>0.0</td>
<td>11.3 (1.6; 79.9)/1</td>
</tr>
<tr>
<td>8</td>
<td>...</td>
<td>...</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>9</td>
<td>...</td>
<td>...</td>
<td>0.0</td>
<td>0.0</td>
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Test for trend P<0.0001 P<0.0001 P<0.0001 P<0.0001
CI indicates confidence interval.
groups were of equal size, the use of the CHA$_{2}$DS$_{2}$VASc score instead of the CHADS$_{2}$ score would reclassify more patients incorrectly than correct; however, this reclassification would be for the benefit of the patients at high risk of stroke.

In detecting patients actually in risk using the NRI, the CHA$_{2}$DS$_{2}$VASc risk score showed superiority compared with the CHADS$_{2}$ score, by shifting 39% of the nonevent patients from the CHADS$_{2}$ low-risk group to the CHA$_{2}$DS$_{2}$VASc in-risk group (Figures 5 and 6). Of the atrial fibrillation patients having an event within 1 year, 17% would correctly be transferred to the in-risk group, using the CHA$_{2}$DS$_{2}$VASc score. After 5-year follow-up, this event rate was increased to 32%. At 1-year follow-up, the ratio of reclassified patients who had a stroke relative to those who did not was 1:27, whereas at 5-year follow-up, this ratio was 1:9, meaning that for every 1 stroke, 27 and 9, respectively, should have received treatment without getting an event of those additionally put on treatment by using CHA$_{2}$DS$_{2}$VASc instead of CHADS$_{2}$. Using a zero score to represent a low-risk group in both CHADS$_{2}$ and CHA$_{2}$DS$_{2}$VASc scores, no CHADS$_{2}$ in-risk patients would incorrectly be transferred to the CHA$_{2}$DS$_{2}$VASc low-risk group because CHADS$_{2}$ is a subset of CHA$_{2}$DS$_{2}$VASc risk score.

**Discussion**

In this study, which is based on a prospective epidemiological cohort of 1603 nonanticoagulated atrial fibrillation patients, we found that the CHADS$_{2}$ as well as the CHA$_{2}$DS$_{2}$VASc risk score can exclude a large proportion of patients from having high risk of stroke or death. Using the CHA$_{2}$DS$_{2}$VASc risk score, fewer patients will fulfill the criterion for low risk (and are truly low risk) and the predictive negative value is increased. In detecting patients actually in risk using the CHA$_{2}$DS$_{2}$VASc risk score, the NRI showed superiority for this risk score compared with the CHADS$_{2}$ score; indeed, by
correctly “upgrading” nearly one-third of the patients with stroke to the high-risk group, it would probably have been possible to prevent some of these adverse outcomes if the patient had been offered proper antithrombotic therapy. This is, however, at the cost of an additional number of patients on therapy who would never have a stroke.

Time-dependent areas under the ROC curves, providing accurate information of time from incident atrial fibrillation to primary event, and the diagnostic performances of the 2 prediction rules were similar during the entire follow-up period (Figures 1 and 2). The AUCs evaluated after 1-year follow-up were 0.68 (0.59–0.76) for CHADS2 and 0.69 (0.60–0.77) for CHA2DS2-VASc. When compared with the c-statistics for CHADS2 found in the Euro Heart Survey analysis of 0.56 (0.45–0.67), there were a bit higher values at this point, probably because the classification in the Euro Heart Survey was ternary (low, intermediate, and high) for the ROC curve analysis and probably also because nearly one-third was lost to follow-up in this survey, with the risk of overlooking patients with stroke or death. In a large nationwide study of Danish patients admitted to a hospital with atrial fibrillation, patients categorized into low-, intermediate-, and high-risk groups, had a c-statistics at 10 years’ follow-up of 0.81 (0.80–0.83) with CHADS2 and 0.89 (0.88–0.90) categorized with the CHA2DS2-VASc risk score, respectively.

The c-statistics in the present study were not statistically different, and this method provides no information on whether there is a correct classification in the desired direction—for example, when the purpose is to identify true noncases. The NRI seems to be a valuable supplement to the c-statistic and NPV in evaluating the added predictive ability of the CHA2DS2-VASc score. With the focus on reclassification of the individual level, the NRI can contribute to a more meaningful evaluation of the clinical utility of this novel risk score with the assumed high-risk definition.
Indeed, one of the pitfalls of using AUC is that very large differences in AUC are required for a direct comparison. This could lead to a false interpretation of AUC irrespective of wide confidence intervals. Therefore, the use of the NRI can contribute to a much more meaningful estimate of the clinical utility of this novel risk score.

Using the NRI, we have shown that a CHA2DS2VASc score of ≥1 could appropriately reclassify 32% of true cases of atrial fibrillation after 5 years of treatment. This will also lead to an excess of noncases classified as cases. We believe that the benefits for stroke prevention outweigh the impact of classifying noncases as cases. The application of the CHA2DS2VASc risk score leads to a clinically important improvement in the identification of patients in risk as well as patients at very low risk for stroke.

After 1-year follow-up in this cohort of 1603 nonanticoagulated atrial fibrillation patients (967 men and 636 women), the incidences of stroke and death were 3.4 and 13.6 per 100 person-years. These data are similar to what was seen in the Danish cohort from Olesen et al,10 except there was a higher death rate in our study that was probably attributed to the fact that their study excluded patients who died within 7 days from discharge. In the Euro Heart Survey, the combined incidence of stroke and thromboembolism after 1 year was 5.9% and 2.0%, respectively.7 However, in the latter study, approximately 30% of the patients were lost to follow-up after 1 year.

A trend, although statistically insignificant, was seen for the CHA2DS2VASc (Figure 2) in the ability of identifying the truly low-risk patients after 1 year follow-up, in whom no antithrombotic therapy is recommended. For comparison, the study by Olesen et al10 reported that patients with a CHA2DS2VASc score of zero had an annual incidence rate of thromboembolism or death of only 0.78 per 100 person-years, which was lower than our findings showing incidence rates for stroke and death of 0.9 and 8.5, respectively (Table 4 and Table 5, respectively). In our study, however, we included all-cause mortality and would therefore expect a higher incidence. In any case, it is essential to bear in mind what affects the predictive values in a diagnostic test. When a condition changes toward a lower prevalence, it will in this case alter the NPV in a positive direction. When more variables are introduced to a prediction rule, fewer patients will fulfill the criterion for a negative score. Furthermore, following the curves in Figures 3 and 4, it is evident that the NPV will decrease over time. Consequently, it is probably advisable to perform clinical follow-up on a regular basis for patients with a negative risk score.

Given the high mortality and morbidity associated with atrial fibrillation–related thromboembolism, a stroke risk score that is more inclusive of common stroke risk factors (ie, CHA2DS2VASc) would have “flagged up” more patients for anticoagulant treatment, which would have the potential to reduce stroke risk in these individuals. Our results suggest that for every 10 extra patients transferred to the treatment group at 5 years, 1 would have had a stroke that might have been avoided with effective treatment.

The serious consequence in terms of disability and death from stroke is significantly higher than a side effect in the form of bleeding (intracranial hemorrhage not included), also from an economic perspective.18 A Markov decision analysis model recently proposed that with the availability of new, “safer” oral anticoagulant drugs, the tipping point balancing the relative hazard of ischemic stroke to the relative hazard of intracranial hemorrhage would change so that an oral anticoagulant is the preferred therapy at stroke rates of 0.9% per year and above compared with aspirin or no therapy at all.19 Aspirin is only minimally effective and carries a significant hazard, with the risk of major bleeding or intracranial hemorrhage similar to warfarin, especially in the elderly. The recent study by Olesen et al10 found no net clinical benefit for aspirin at any level of stroke risk, whereas the net clinical benefit for warfarin (versus untreated) was only negative at a CHA2DS2VASc score=0, reflecting the truly low-risk status of such patients.

The main strengths of our study are the prospective design and the large number of stroke events, as well as the complete and extended follow-up through nationwide, population-based registries, limiting the risk of selection and surveillance bias. The method used provides accurate information of time from incident atrial fibrillation to primary event. Furthermore, we have a standardized assessment of all registered outcome events using the ICD codes in a nondifferentially manner as proposed by others.20 The positive predictive value of the diagnosis of atrial fibrillation is as high as 99% in the registry.21 Ischemic stroke also had a positive predictive value of 87.6% in the Danish registry,9 and data on prescription claims are very accurate.22 The results from the present study are similar to and broadly comparable with the results from the Non-Rheumatic Atrial Fibrillation registry (NRAF), which was initially used to validate the CHADS2 score.3 The results from the present study also represent an everyday real-life scenario, but it is still surprising and alarming that so many patients with a CHADS2 score of ≥2 (>20%) did not receive oral anticoagulation.

**Limitations**

The limitations of this study are its observational design, on a cohort of invited participants. We know from other studies that such participants generally tend to be healthier and less uninformed than the background population, which is also true for the Danish Diet, Cancer, and Health cohort study.14 Using register-based ICD codes, it was not possible to differentiate between paroxysmal, persistent, lone, or permanent atrial fibrillation. Also, the reliance on ICD codes to identify the presence of the components of these risk scores may have resulted in incorrect calculation of these scores compared with a physician’s assessment; however, this would be intrinsic to many other similar studies investigating stroke risk in atrial fibrillation using administrative datasets or cohorts. Furthermore, the overall incidence rates of atrial fibrillation and stroke in this study are comparable with the incidence rates found in similar studies.7,9

This study is based on 1603 subjects who were not anticoagulated 180 days before an event or at the end of follow-up, and thus, the study population could be biased by excluding lower-risk patients already selected for anticoagulation. These patients could be younger and have lower
bleeding risk and fewer comorbid conditions, resulting in an underrepresentation of those aged older than 75 years. On the other hand, this increases the possibility that we might have included some patients who were not started on oral anticoagulant therapy because of comorbidities, poor compliance (or inability to have adequate monitoring), and/or intolerance of anticoagulation. However, it is unlikely that selection bias has seriously influenced our results because the incidences of outcomes are comparable with other studies according to the above discussion.

Conclusion
Many of the patients at low risk according to CHADS2 are not at "truly low risk." However, in this population of nonanti-coagulated patients with atrial fibrillation, both the CHADS2 as well as the CHA2DS2VASc risk score could exclude a large proportion of patients from having high risk of stroke or death. Using the CHA2DS2VASc risk score, fewer patients would fulfill the criterion for low risk (and are truly low risk for thromboembolism). Given the high mortality and morbidity rates associated with atrial fibrillation–related thromboembolism, the CHA2DS2VASc stroke risk score is more inclusive of common stroke risk factors and would have "flagged up" more patients for anticoagulant treatment, which would have the potential to reduce stroke risk in these individuals.

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Disclosures
None.

References
Added Predictive Ability of the CHA$_2$DS$_2$VASc Risk Score for Stroke and Death in Patients With Atrial Fibrillation: The Prøspective Danish Diet, Cancer, and Health Cohort Study

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### SUPPLEMENTAL MATERIAL

Web-only - Table w1. Cohort exposure assessment

<table>
<thead>
<tr>
<th>CHADS$_2$ &amp; CHA$_2$DS$_2$VASC</th>
<th>ICD 8</th>
<th>ICD 10</th>
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</thead>
<tbody>
<tr>
<td>Stroke*</td>
<td>433.09, 433.99, 434.09, 434.99, 436.01, 436.90</td>
<td>I63.0 – I63.9, I64.9</td>
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<tr>
<td>Transient ischemic attack</td>
<td>435.09, 435.99</td>
<td>G45.0 – G45.9**</td>
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<tr>
<td>Thromboembolism</td>
<td>444.00 – 444.99</td>
<td>I74.0 – I74.9</td>
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<tr>
<td>Congestive heart failure</td>
<td>427.09, 427.10, 427.11, 427.19</td>
<td>I50.0 – I50.9, I11.0</td>
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<td>LV Dysfunction</td>
<td>427.10</td>
<td>I50.1, I50.9</td>
</tr>
<tr>
<td>Diabetes mellitus (type I)</td>
<td>249.00, 249.09</td>
<td>E10.0 – E10.9</td>
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<tr>
<td>Diabetes mellitus (type II)</td>
<td>250.08, 250.09</td>
<td>E11.0 – E11.9</td>
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<tr>
<td>Diabetes with no specification</td>
<td>-</td>
<td>E14.0 – E14.9</td>
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<tr>
<td>Acute Myocardial Infarct</td>
<td>410.09, 410.99</td>
<td>I21.0 – I21.9, I22.0 – I22.9</td>
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<td>Peripheral Arterial Disease</td>
<td>440.20, 443.99, 444.41</td>
<td>I70.2, I73.9, I74.5</td>
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<tr>
<td>Aortic Plaque</td>
<td>440.09</td>
<td>I70.0</td>
</tr>
</tbody>
</table>

ICD: International Classification of Diseases
*430, 431 (ICD-8) & I60-I62 (ICD-10) not included (haemorrhagic stroke)
** Not inclusive G45.3 (Amaurosis fugax)