A risk stratification scoring system for new-onset atrial fibrillation after ischemic stroke

A National cohort study

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Abstract
Atrial fibrillation (AF) is a major independent risk factor of stroke and anticoagulation therapy is needed in patients with AF after ischemic stroke. However, the detection rate of AF is low after ischemic stroke. Developing a prediction model for newly diagnosed AF after ischemic stroke will help to assess the subclinical AF.

We identified 98,103 patients with diabetes mellitus (DM) and 261,893 patients without DM, who were not AF history and admitted for newly ischemic stroke from the National Health Insurance Research Database in Taiwan. The prediction model for 3-year incidence of AF after ischemic stroke was derived from multivariate logistic regression and also the accuracy rate of the prediction model was compared with CHA\textsubscript{2}DS\textsubscript{2}-VASc and CHADS\textsubscript{2} scores as a reference.

Four thousand nine hundred seventy six patients in the DM cohort and 16,127 patients in the non-DM cohort developed AF during 3 years of follow-up. The variables in the point-based prediction model for non-DM patients (range: -3–28), included age, heart failure, coronary artery disease, gout, obstructive pulmonary disease, hypertension, female, and statin use, while those for DM patients (range: -2–30) included age, heart failure, coronary artery disease, chronic kidney disease, hypertension, obstructive pulmonary disease, and statin use. Compared to the CHADS\textsubscript{2} and CHA2DS\textsubscript{2}-VASc scoring systems, this scoring system was better at predicting 3-year risk of AF after ischemic stroke in both cohorts.

This model might be useful in evaluating the benefit of insertable cardiac monitor implantation and anticoagulation agents in individual patients after ischemic stroke.

Abbreviations: AF = atrial fibrillation, AUC = area under receiver operating characteristic curves, CAD = coronary artery disease, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HF = heart failure, HTN = hypertension, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, PAOD = peripheral artery occlusive disease, PPV = positive predictive value.

Keywords: anticoagulation, atrial fibrillation, ischemic stroke, prediction model, stroke

1. Introduction
Atrial fibrillation (AF) is associated with an increased risk of stroke and about 20% to 30% of patients with ischemic stroke are diagnosed with AF before, during or after the event.\textsuperscript{[1]} Patients with stroke due to AF have a worse clinical outcome than patients with stroke due to other factors.\textsuperscript{[2]} Anticoagulation decreased the risk of new-onset and recurrent stroke in AF patients.\textsuperscript{[3]} The choice of anticoagulation therapy is totally different for stroke patients with and without AF.\textsuperscript{[4,5]} In addition, rivaroxaban for stroke prevention after embolic stroke with undetermined source was not superior and even more risk of
bleeding than aspirin. Therefore, the diagnosis and early detection of AF is important, especially in patients after stroke. Current clinical guidelines suggest prolonged electrocardiographic monitoring (e.g., a 72-hour Holter recording) for stroke patients to enhance the detection of undiagnosed AF. However, even an implantable loop recorder and prolonged Holter recording could detect only 15% to 20% of AF in ischemic stroke patients within 6 months and 2 years. Risk stratification for ischemic stroke patients may be helpful in determining high-risk AF patients, and also in identifying candidates for aggressive clinical monitoring. Previous studies showed the that prevalence of diabetes mellitus (DM) was lower in AF patients with stroke than in non-AF patients with stroke and that there were different stroke patterns in DM and non-DM patients, so we analyzed risk stratification in both DM and non-DM cohorts, in an attempt to avoid the interaction of DM and AF occurrence in stroke patients. The aim of this study was to develop a risk stratification system to identify DM and non-DM patients at high risk of developing AF after ischemic stroke.

2. Methods

2.1. Data sources

This national cohort study utilized data on stroke patients retrieved from Taiwan’s National Health Insurance Research Database (NHIRD) from January 1, 2001 to December 31, 2013. The NHIRD is part of Taiwan’s National Health Insurance program, which is a compulsory single-payer healthcare system covering more than 20 million Taiwanese, and contains health care information dating back to 1997. NHIRD includes data of any outpatient visits, hospitalization, drug prescriptions, comorbidities, and vital status. In addition, identifying data of all participants were encrypted to protect their privacy, but they can be longitudinally followed since the encrypting procedure was consistent. Diseases were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Our study population was coded as ICD-9-CM: 433–435, those who had experienced an ischemic stroke event. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (201701617B0).

2.2. Study population in 2 prediction models

A total of 471,048 subjects admitted to the hospital with a principal diagnosis of ischemic stroke between January 1, 2001 and December 31, 2013 were identified for this study. Patients aged <40 years were excluded. In order to evaluate the post-stroke incidence of AF, patients who were diagnosed with AF before or at the time of hospitalization for index ischemic stroke were excluded. In order to limit the type of index ischemic stroke to unknown etiology, the following exclusion criteria were set in this study. Patients who were diagnosed with carotid disease, including stenting for carotid arteries, and those who were diagnosed with cerebral arterial aneurysm or arteriovenous fistula or stenosis of the cerebrovascular arteries, were excluded.

In addition, those who were diagnosed with valvular heart disease, rheumatic heart disease, and hyperthyroidism, and who had been given long-term anticoagulation agents, were also excluded. Patients who died during the index hospitalization were excluded from the analysis. In the end, 359,996 patients were eligible for analysis. Although DM was a strong predictor of AF, several studies showed the incidence of AF was inconsistent in DM patients admitted for ischemic stroke and the incidence of stroke associated with atherothrombotic disease was higher than stroke associated with cardioembolic disease in the DM population. Therefore, we used 2 prediction models to predict the development of new-onset AF after ischemic stroke: 1 for DM patients and the other for non-DM patients. Finally, 98,103 DM patients and 261,893 non-DM patients who were admitted for ischemic stroke, respectively, were included in the study.

2.3. Ascertainment of ischemic stroke, AF, and comorbidities

The index event of ischemic stroke was based on the principal diagnosis (ICD-9-CM: 433–435), meaning that the index hospitalization was for ischemic stroke. The positive predictive value (PPV) of ischemic stroke in the AF population was close to 95% in our previous study. AF was diagnosed according to the diagnostic code of AF (ICD-9-CM: 42731) in 1 admission or consecutive 2 outpatient visits and its PPV was around 90% in previous validation. Besides, inpatient and outpatient diagnosis and prescription data during the 12-month period before the index date to ascertain the other comorbidities (ICD-9-CM codes proved in Supplemental Table S1, http://links.lww.com/MD/E430). The definitions of comorbidities were the same criteria as AF as was listed in Supplemental Table S1, http://links.lww.com/MD/E430. Similarly, the medication was ascertained. (Anatomical Therapeutic Chemical code provided in Supplemental Table S1, http://links.lww.com/MD/E430) Data on patients who suffered from AF development 3 years after the index ischemic stroke event were censored. Data on patients who died within 3 years after the index date were also censored.

2.4. CHA2DS2-VASc and CHADS2 scores as a referent model

CHA2DS2-VASc and CHADS2 scores were used to predict the incidence of stroke in non-rheumatic AF, and they were also used to predict the incidence of AF in some studies. Therefore, these 2 scoring systems were used for comparison (a referent model) with our proposed scoring system. The CHA2DS2-VASc score involves a point system in which 2 points were assigned for a history of stroke or transient ischemic attack or age ≥75 years, and 1 point each was assigned for those aged 65 to 74 years or with a history of hypertension (HTN), diabetes, heart failure (HF), vascular disease (myocardial infarction or peripheral artery disease), and female gender. In the CHADS2 scoring system, 2 points were assigned for a history of stroke or transient ischemic attack and 1 point each for the presence of HTN, diabetes, congestive HF, and age ≥75 years.

2.5. Statistical analyses

We compared the distribution of baseline characteristics between the AF and non-AF patients using the t test for continuous variables and Chi-Squared test for categorical variables. To investigate the factors associated with the risk of AF development, we performed Cox proportional hazard models in 3 steps. First, each variable (a total of 12) was studied as an independent variable in the univariate analyses. Second, the significant variables (P < 0.05) in the univariate analyses were further introduced into the multivariable Cox model. Third, to achieve
a parsimonious and easy-to-use model, non-significant variables were dropped in a reduced model.

To examine the problem of over-fitting in the reduced model, internal validation was performed using the bootstrap method with 200 bootstrapped samples to compare the area under receiver operating characteristic curves (AUC) between the original model (optimistic) and the bootstrap-corrected model. To assess the extent of discriminating AF development, we compared the AUC between our proposed scoring system and the existing scoring systems (CHADS2 and CHA2DS2-VASc scores). Based on the results of the reduced multivariable model, we calculated a simplified point system to demonstrate the associations between explanatory variables (covariates) and incident AF during a 3-year follow-up. Briefly, the points system rounds off the regression coefficients obtained from the multivariable Cox model. In the first step, a continuous predictor (i.e., age) with a wide range of values was treated as the reference variable and categorized into clinically relevant categories (i.e., <55 yrs., 55–64 yrs., 65–74 yrs., ≥75 yrs.). Next, the reference value of each category of each predictor was calculated according to the value of its regression coefficient (i.e., female gender) relative to that of the reference variable. Finally, as a form of sensitivity analysis, we categorized the patients into 4 groups according to their prediction scores and compared the risk of recurrent ischemic stroke during a 13-year follow-up using a trend test of the log-rank test. A P value of <.05 was considered statistically significant. Data analysis was conducted using commercial software (SAS 9.4, SAS Institute, Cary, NC).

### 3. Results

#### 3.1. Baseline characteristics of DM and non-DM patients with ischemic stroke with and without the occurrence of AF

A total of 359,996 patients were included in the study. Among this group, 98,103 had DM and 261,893 did not; 4976 of the DM patients and 16,127 of the non-DM patients, respectively, developed AF within a 3-year follow-up after ischemic stroke (Supplemental Fig. 1, http://links.lww.com/MD/E430). The differences in baseline characteristics among the patients with and without AF in the DM and non-DM cohort are shown (Supplemental Table S2, http://links.lww.com/MD/E430). Briefly, AF patients were older than non-AF patients in both cohorts. Comorbidities (except for dialysis in both cohorts, and chronic kidney disease (CKD) and peripheral artery occlusive disease (PAOD) in the DM cohort) and medications were significantly different for AF and non-AF patients in both cohorts. Patients who developed AF during follow-up had old myocardial infarct, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), gout, HTN, HF, dyslipidemia, and old stroke more frequently than patients who did not develop AF in both cohorts. Abnormal liver function tests were less frequently noted in patients who developed AF during follow-up than in patients who did not develop AF in both cohorts. Patients who developed AF had more CAD and PAOD than those who did not develop AF in the non-DM cohort. Regarding medication use, patients who developed AF received angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, calcium channel blocker, and beta-blocker more frequently, and statin therapy less frequently than those who did not develop AF in both cohorts.

#### 3.2. Clinical factors associated with risk of AF development after ischemic stroke

The univariate and multivariable analyses of clinical factors associated with the risk of developing AF after ischemic stroke are shown in Table 1. Twelve factors were significant in univariate analyses and were further introduced into the multivariable analyses of both the DM and non-DM cohorts. Seven independent factors (age, CAD, CKD, COPD, HTN, HF, and statin use) in the DM cohort and 8 independent factors (age, female, CAD, COPD, gout, HTN, HF, and statin use) in the non-DM cohort were significantly associated with the occurrence of AF after ischemic stroke during a 3-year follow-up. The predictors in the DM cohort, with the exception of statin, were positively associated with an increasing risk of developing AF during follow-up, after ischemic stroke. Statin was associated with a decreasing risk of AF after ischemic stroke in both the DM and non-DM cohorts.

#### 3.3. Bootstrapping validation of the proposed model

For the reduced multivariable model, the optimistic AUC was 62.99% and 67.05%, and the optimism correction using 200 bootstrapped samples was 0.16% and 0.03% in the DM and non-DM cohorts, respectively. This small discrepancy between the AUC obtained from the original model and that obtained using the bootstrap method indicated that over-fitting might be not an issue.

#### 3.4. Comparisons of other scoring systems with the proposed scoring system

Figure 1 compare the AUCs for different risk scoring systems used to predict a 3-year AF risk after ischemic stroke in the DM and non-DM cohort. Figure 1A shows that, for predicting AF occurrence in DM patients with ischemic stroke, the c-indexes (AUC) were 0.576 (95% confidence interval [CI], 0.568–0.583) for CHADS2, 0.607 (95% CI, 0.600–0.615) for CHA2DS2-VASc, and 0.630 (95% CI, 0.623–0.638) for the proposed model. The ability of the proposed model to discriminate AF occurrence was superior to that of the CHADS2 and CHA2DS2-VASc scores (P of delta AUC < .001). Figure 1B shows similar results for non-DM patients, in that the proposed model (0.671; 95% CI, 0.667–0.675) had a higher AUC than the CHADS2 (0.600; 95% CI, 0.596–0.604) and CHA2DS2-VASc (0.636; 95% CI, 0.632–0.640) scoring systems.

#### 3.5. Simple point systems for the risk of AF development after ischemic stroke

The simple point systems and risk of AF according to the reduced model of patients with and without DM are shown in Tables 2 and 3. Table 2 shows the points of a single predictor and the total scores of AF among patients with DM (total score: 30 points). Because of the reduced risk of AF with statin use, statin use was given -2 points. The total score ranged from -2 to 30. The risk of developing AF within 3 years ranged from 1.7% (score: -2) to 27.6% (score: 30). The optimal cutoff point was 15 with a sensitivity of 58.5% (95% CI: 57.2%–59.9%) and a
Table 1
Factors associated with risk of atrial fibrillation after ischemic stroke in patients with/without diabetes mellitus.

| Characteristics                  | Univariate model | Multivariable model | Reduced multivariable model |
|----------------------------------|------------------|---------------------|-----------------------------|
|                                  | B    | HR    | 95% CI | P value | B    | HR    | 95% CI | P value | B    | HR    | 95% CI | P value |
| DM                               |      |       |        |         |      |       |        |         |      |       |        |         |
| Age (per 10 years)               | 0.500 | 1.65  | 1.60–1.70 | <.001 | 0.452 | 1.57  | 1.52–1.62 | <.001 | 0.457 | 1.58  | 1.53–1.63 | <.001 |
| Female gender                    | 0.120 | 1.13  | 1.07–1.19 | <.001 | 0.030 | 1.03  | 0.97–1.09 | .294 |       |       |        |         |
| Coronary artery disease          | 0.508 | 1.66  | 1.57–1.76 | <.001 | 0.342 | 1.41  | 1.33–1.50 | <.001 | 0.341 | 1.41  | 1.33–1.50 | <.001 |
| Chronic kidney disease           | 0.337 | 1.40  | 1.27–1.55 | <.001 | 0.224 | 1.25  | 1.13–1.38 | <.001 | 0.228 | 1.26  | 1.14–1.39 | <.001 |
| COPD                             | 0.368 | 1.45  | 1.32–1.58 | <.001 | 0.102 | 1.11  | 1.01–1.21 | .024 |       |       |        |         |
| Gout                             | 0.133 | 1.14  | 1.04–1.25 | .005 | 0.100 | 1.08  | 0.99–1.19 | .095 |       |       |        |         |
| Peripheral arterial disease      | 0.176 | 1.19  | 1.05–1.35 | .007 | 0.042 | 1.04  | 0.92–1.19 | .517 |       |       |        |         |
| Hypertension                     | 0.481 | 1.62  | 1.46–1.80 | <.001 | 0.295 | 1.34  | 1.21–1.50 | <.001 | 0.304 | 1.36  | 1.22–1.51 | <.001 |
| Heart failure                    | 0.788 | 2.20  | 2.01–2.41 | <.001 | 0.462 | 1.59  | 1.44–1.75 | <.001 | 0.471 | 1.60  | 1.46–1.76 | <.001 |
| Stroke                           | −0.263 | 0.77  | 0.72–0.82 | <.001 | −0.153 | 0.86  | 0.81–0.92 | <.001 | −0.149 | 0.86  | 0.81–0.92 | <.001 |
| Abnormal liver function          | −0.178 | 0.84  | 0.76–0.92 | <.001 | −0.085 | 0.92  | 0.84–1.01 | .071 |       |       |        |         |
| Old stroke                       | 0.205 | 1.23  | 1.14–1.33 | <.001 | 0.068 | 1.07  | 0.99–1.16 | .089 |       |       |        |         |
| Non-DM                           |      |       |        |         |      |       |        |         |      |       |        |         |
| Age (per 10 years)               | 0.572 | 1.77  | 1.75–1.80 | <.001 | 0.522 | 1.69  | 1.66–1.71 | <.001 | 0.522 | 1.69  | 1.66–1.71 | <.001 |
| Female gender                    | 0.166 | 1.18  | 1.15–1.22 | <.001 | 0.038 | 1.04  | 1.01–1.07 | .022 | 0.038 | 1.04  | 1.01–1.07 | .022 |
| Coronary artery disease          | 0.620 | 1.86  | 1.80–1.92 | <.001 | 0.381 | 1.46  | 1.41–1.52 | <.001 | 0.380 | 1.46  | 1.41–1.51 | <.001 |
| Chronic kidney disease           | 0.359 | 1.43  | 1.32–1.55 | <.001 | 0.047 | 1.05  | 0.97–1.14 | .255 |       |       |        |         |
| COPD                             | 0.540 | 1.72  | 1.64–1.79 | <.001 | 0.123 | 1.13  | 1.08–1.18 | <.001 | 0.121 | 1.13  | 1.08–1.18 | <.001 |
| Gout                             | 0.259 | 1.30  | 1.24–1.36 | <.001 | 0.194 | 1.21  | 1.16–1.27 | <.001 | 0.196 | 1.22  | 1.16–1.28 | <.001 |
| Peripheral arterial disease      | 0.258 | 1.29  | 1.19–1.41 | <.001 | −0.025 | 0.98  | 0.89–1.06 | .574 |       |       |        |         |
| Hypertension                     | 0.235 | 1.27  | 1.22–1.31 | <.001 | 0.061 | 1.06  | 1.02–1.10 | .002 | 0.060 | 1.06  | 1.02–1.10 | .002 |
| Heart failure                    | 0.948 | 2.58  | 2.43–2.75 | <.001 | 0.442 | 1.56  | 1.46–1.66 | <.001 | 0.441 | 1.56  | 1.46–1.66 | <.001 |
| Stroke                           | −0.477 | 0.62  | 0.60–0.65 | <.001 | −0.292 | 0.75  | 0.72–0.78 | <.001 | −0.291 | 0.75  | 0.72–0.78 | <.001 |
| Abnormal liver function          | −0.074 | 0.93  | 0.88–0.98 | .009 | −0.007 | 0.99  | 0.94–1.05 | .801 |       |       |        |         |
| Old stroke                       | 0.230 | 1.26  | 1.20–1.32 | <.001 | −0.027 | 0.97  | 0.93–1.02 | .290 |       |       |        |         |

B indicates regression coefficient.

For the reduced multivariable model in DM population, the optimistic area under ROC (AUC) was 62.99% and bootstrapped optimism correction (using 200 bootstrap samples) was 0.16%, resulting in a corrected AUC of 62.83%.

For the reduced multivariable model in Non-DM population, the optimistic area under ROC (AUC) was 67.05% and bootstrapped optimism correction (using 200 bootstrap samples) was 0.03%, resulting in a corrected AUC of 67.02%.

HR = hazard ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus.

Figure 1. Receiver operating characteristic (ROC) curves of 3 different risk scoring systems in predicting a 3-year atrial fibrillation risk after ischemic stroke in the diabetes mellitus (DM) (A) and non-DM (B) cohort. 1A. ROC curves of the proposed model (area under the curve [AUC], 0.630; 95% confidence interval [CI], 0.623–0.638), CHADS2 (AUC, 0.576; 95% CI, 0.568–0.583) and CHA2DS2-VASc (AUC, 0.607; 95% CI, 0.600–0.615) in DM cohort. The AUC was significantly larger in the proposed model than in the CHADS2 and CHA2DS2-VASc (both P of delta AUC < .001). 1B. ROC curves of the proposed model (area under the curve [AUC], 0.671; 95% confidence interval [CI], 0.667–0.675), CHADS2 (AUC, 0.600; 95% CI, 0.596–0.604) and CHA2DS2-VASc (AUC, 0.636; 95% CI, 0.632–0.640) in non-DM cohort. The AUC was significantly larger in the proposed model than in the CHADS2 and CHA2DS2-VASc (both P of delta AUC < .001).
specificity of 60.0% (95% CI: 59.7%–60.3%). Table 3 shows the points of a single predictor and the total points and risk of AF in patients without DM (total score: 28 points). The total score ranged from −3 to 28. The risk of developing AF within 3 years ranged from 1.7% (score: −3) to 35.5% (score: 28). The optimal cutoff point was 12 with a sensitivity of 71.3% (95% CI: 70.6%–72.0%) and a specificity of 53.3% (95% CI: 53.1%–53.5%).

3.6. Simple points system for risk of recurrent stroke

The values of the simple points system were divided into 4 groups (quartiles), and the risk of recurrent stroke was compared among groups. Figure 2 shows that the risk of recurrent stroke was higher when the predicting scores increased in both the DM and non-DM cohorts ($P_{trend} < .001$).

4. Discussion

There are several important findings in this study. First, patients with ischemic stroke who developed AF rhythm were older and had more comorbidity, whether in the DM or non-DM cohort. Second, patients with ischemic stroke who received statin therapy less frequently had AF rhythm during follow-up. Third, our scoring system was better at predicting AF occurrence after ischemic stroke than the CHADS2 score and CHA2DS2-VASc score. Finally, those patients who had a higher score had a higher

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**Table 2**

Simple points system according to the reduced model of patients with diabetes mellitus (Total score 30 points).

| Single predictor                  | Point | Points total | Risk | Points total | Risk |
|-----------------------------------|-------|--------------|------|--------------|------|
| Age, years                        |       |              |      |              |      |
| <55                               | 0     | −2           | 0.017| 14           | 0.072|
| 55–64                             | 5     | −1           | 0.019| 15           | 0.078|
| 65–74                             | 10    | 1            | 0.021| 16           | 0.086|
| ≥ 75                              | 15    | 2            | 0.022| 17           | 0.093|
| Coronary artery disease           | Yes   | 4            | 0.025| 18           | 0.102|
| Chronic kidney disease            | Yes   | 2            | 0.027| 19           | 0.111|
| Chronic obstructive pulmonary disease | Yes  | 1            | 0.029| 20           | 0.121|
| Hypertension                      | Yes   | 3            | 0.032| 21           | 0.132|
| Heart failure                     | Yes   | 5            | 0.036| 22           | 0.144|
| Statin                            | Yes   | −2           | 0.040| 23           | 0.156|
| Gender                            | Female| 1            | 0.046| 24           | 0.170|
| Coronary artery disease           | Yes   | 4            | 0.050| 25           | 0.185|
| Chronic obstructive pulmonary disease | Yes  | 1            | 0.055| 26           | 0.200|
| Gout                              | Yes   | 5            | 0.060| 27           | 0.217|
| Hypertension                      | Yes   | 6            | 0.066| 28           | 0.236|
| Heart failure                     | Yes   | 7            | 0.066| 29           | 0.255|
| Statin                            | Yes   | −2           | 0.072| 30           | 0.276|

The optimal cutoff point was 15 with a sensitivity of 58.5% (57.2%–59.8%) and a specificity of 60.0% (59.7%–60.3%).

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**Table 3**

Simple points system according to the reduced model of patients without diabetes mellitus (Total score 28 points).

| Single predictor                  | Point | Points total | Risk | Points total | Risk |
|-----------------------------------|-------|--------------|------|--------------|------|
| Age, years                        |       |              |      |              |      |
| <55                               | 0     | −3           | 0.017| 13           | 0.087|
| 55–64                             | 5     | −2           | 0.019| 14           | 0.097|
| 65–74                             | 10    | −1           | 0.021| 15           | 0.107|
| ≥ 75                              | 15    | 0            | 0.023| 16           | 0.118|
| Gender                            | Female| 1            | 0.026| 17           | 0.130|
| Coronary artery disease           | Yes   | 4            | 0.029| 18           | 0.143|
| Chronic obstructive pulmonary disease | Yes  | 1            | 0.032| 19           | 0.157|
| Gout                              | Yes   | 5            | 0.036| 20           | 0.173|
| Hypertension                      | Yes   | 6            | 0.039| 21           | 0.190|
| Heart failure                     | Yes   | 7            | 0.043| 22           | 0.209|
| Statin                            | Yes   | −3           | 0.053| 23           | 0.229|

The optimal cutoff point was 12 with a sensitivity of 71.3% (70.6%–72.0%) and a specificity of 53.3% (53.1%–53.5%).
risk of recurrent stroke than those patients who had a lower score.

4.1. Risk factors for patients in both cohorts with ischemic stroke developing AF during follow-up

Our study showed that patients with ischemic stroke shared the same risk factors for AF occurrence in both cohorts (age, HTN, HF, CAD). In clinical practice, these risk factors are common among patients at risk for silent AF.[12] A previous study reported the adjusted hazard ratio for AF among those with COPD was 2.23 compared to those without COPD, irrespective of DM.[13] The chronic inflammation status, hypoxemia and cardiac remodeling due to COPD may explain the increased risk of AF in COPD patients. In our study, COPD was an independent predictor of AF in patients with ischemic stroke. Our study also found that CKD was an independent factor for developing AF in ischemic stroke patients with DM. CKD is associated with insulin resistance and insulin resistance has been associated with increased risk of AF.[14] Although men have a higher incidence of AF,[15] women with AF have double the risk of stroke compared to men, after adjustment for other comorbidity.[16] This may explain the higher risk of female gender in predicting AF after ischemic stroke. The systemic inflammation and impact of left atrial remodeling of gout may explain its prediction of AF in our study.[17] Previous and current studies show statin use and adherence are associated with a reduced first or recurrent stroke risk in patients with and without AF.[18] Our study, using a large nationwide database, confirms previous findings, and reveals the independent predictors of AF occurrence in patients with ischemic stroke with and without DM.

4.2. A novel scoring system for predicting AF and recurrent stroke in patients with ischemic stroke, irrespective of DM

A previous small cohort study showed CHADS2 and CHA2DS2-VASc scores could predict the risk of AF in patients with ischemic stroke.[19] However, another large study reported no difference among patients with different CHA2DS2-VASc scores in the detection rate of AF using an implantable cardiac monitor.[20] In this study, our novel scoring system performed better than CHADS2 or CHA2DS2-VASc scores in predicting the occurrence of AF after ischemic stroke during traditional clinical follow-up of patients with and without DM. This means our scoring system is more useful in determining those ischemic stroke patients who are truly at high risk of AF incidence. In addition, the risk of recurrent stroke was higher in patients with higher scores in both cohorts, according to our study. Therefore, our scoring system is very helpful in defining patients at a higher risk of AF occurrence and recurrent stroke, which is beneficial to identifying those who need intensified cardiac monitoring or even more aggressive anticoagulation use.

The overall detection rate for any AF after ischemic stroke ranged from 9.5% to 43% in previous studies with different interventions, durations, monitoring methods, and diagnostic criteria for paroxysmal AF and cryptogenic stroke.[1] Prospective studies evaluating invasive cardiac monitoring in small groups of patients with cryptogenic stroke showed varying detection rates (from 4.2% to 40%) during long-term follow-up (14.5 to 36 months).[15,20,21] Detection rates tended to be higher with prolonged periods of monitoring in selected patient groups. However, insertable cardiac monitoring is more expensive and is inconvenient for patients in terms of quality of life. Our study also identified those patients with ischemic stroke who could obtain the most benefit from invasive cardiac monitoring to detect AF, which might influence the decision to initiate anticoagulation use.

4.3. Study limitations

There are some limitations in this retrospective insurance database study. First, there were no echocardiographic variables, including left atrial size, that might predict AF occurrence in stroke patients. However, 1 study showed that echocardiograph-
ic parameters did not improve the risk evaluation for predicting AF, and the accuracy of echocardiographic is highly technician-dependent, and measurement variability between observers is difficult to evaluate, even in a prospective trial with training and central analysis. Therefore, echocardiographic measurement items may not be applicable for risk stratification in a clinical situation, especially with a large cohort population. Second, the subtype of AF was not recorded in the NHIRD database. However, most of the time, the AF type documented in patients with ischemic stroke is paroxysmal AF less than 2 days. Third, neither the CHADS2 nor the CHA2DS2-VASC scores are designed to predict the occurrence of AF, they are intended to predict stroke risk related to AF. It is well known that atrial cardiopathy can induce embolism without the presence of AF. This form of cardiopathy shares many of the described risk factors for AF, suggesting that there might be a pathophysiological continuum between it and AF. Further study is needed to evaluate the relationship and interaction of atrial cardiopathy and AF occurrence. Finally, although our study, using our novel risk scoring system, showed patients with a higher score had a higher risk of recurrent stroke, we did not evaluate the anticoagulation status before recurrent stroke; the use and adhesion of anticoagulation may influence the risk of recurrent stroke. We also did not evaluate the ablation status after occurrence of AF and before recurrent stroke. The different ablation strategies may influence the risk of recurrent AF and also recurrent stroke.

5. Conclusions
This national cohort study showed that our novel risk scoring system might be used to predict AF and recurrent stroke effectively in ischemic stroke patients with or without DM. Patients in both cohorts shared the same risk factors for AF occurrence, including age, HTN, HF, CAD, and COPD. CKD was the independent predictive factor in the DM cohort, female gender, and gout were independent factors in the non-DM cohort. Our novel risk scoring system might be used for evaluation of the benefit of insertable cardiac monitoring and anticoagulation use.

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