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ORIGINAL INVESTIGATIONS

Comparative Performance of ATRIA, $CHADS_2$, and CHA_2DS_2-VASc Risk Scores Predicting Stroke in Patients With Atrial Fibrillation

Results From a National Primary Care Database

Hendrika A. van den Ham, PharmD,* Olaf H. Klungel, PharmD, PhD,* Daniel E. Singer, MD,†
Hubert G.M. Leufkens, PharmD, PhD,* Tjeerd P. van Staa, MD, PhD*‡

ABSTRACT

BACKGROUND Previous studies report that $CHADS_2$ and CHA_2DS_2-VASc risk scores have similar discriminating ability (C statistic ~0.6). Recently a clinically based risk score, the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study risk score, was developed and validated.

OBJECTIVES This study compared predictive ability of CHA_2DS_2-VASc and $CHADS_2$ ischemic stroke risk scores with ATRIA stroke risk score and their implications for anticoagulant treatment in patients with atrial fibrillation (AF).

METHODS Patients with AF not using warfarin were included from the Clinical Practice Research Datalink database, 1998 to 2012. Patients were followed from AF diagnosis until occurrence of ischemic stroke, prescription of warfarin, death, or the study's end. Independent predictors of ischemic stroke were identified and the c-index and net reclassification improvement were calculated.

RESULTS A total of 60,594 patients with AF were included. Annualized stroke rate was 2.99%. Event rates for moderate- and high-risk categories for CHA_2DS_2-VASc were lower than those of the ATRIA and $CHADS_2$. Age and previous stroke most strongly predicted ischemic stroke. C statistics for the full point scores were 0.70 (95% confidence interval [CI]: 0.69 to 0.71) for the ATRIA risk score, 0.68 (95% CI: 0.67 to 0.69) for $CHADS_2$, and 0.68 (95% CI: 0.67 to 0.69) for CHA_2DS_2-VASc risk score. The net reclassification improvement was 0.23 (95% CI: 0.22 to 0.25) for ATRIA compared with CHA_2DS_2-VASc.

CONCLUSIONS The ATRIA score performed better in the U.K. Clinical Practice Research Datalink AF cohort. It more accurately identified low-risk patients than the CHA_2DS_2-VASc score, which assigned these patients to higher-risk categories. Such reclassification of stroke risk could prevent overuse of anticoagulants in very low stroke risk patients with AF. (J Am Coll Cardiol 2015;66:1851–9) © 2015 by the American College of Cardiology Foundation.

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From the *Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; †Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; and the ‡Department of Health eResearch, University of Manchester, Manchester, United Kingdom. Dr. Klungel has received unrestricted funding for pharmacoepidemiological research from the Dutch private-public TI Pharma Mondriaan project. Dr. Singer has served as a consultant to Boehringer Ingelheim, Bristol-Myers Squibb, CVS Health, Johnson and Johnson, Medtronic, and Merck; and has received research support from Boehringer Ingelheim, Bristol-Myers Squibb, and Medtronic. Dr. Leufkens is a researcher at the World Health Organization Collaborating Centre for Pharmaceutical Policy and Regulation, which receives no direct funding or donations from private parties, including pharmaceutical industry. Research funding from public-private partnerships (e.g., IMI, TI Pharma) is accepted under the condition that no company-specific product or company-related study is conducted. The Centre has received

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex

$CHADS_2$ = congestive heart failure, hypertension, age ≥75, diabetes, and stroke

CPRD = Clinical Practice Research Database

GP = general practitioner

HES = Hospital Episode Statistics

NRI = net reclassification index

TIA = transient ischemic attack

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders and is associated with a substantial risk of ischemic stroke and thromboembolism. Various risk factors have been associated with the occurrence of stroke in patients with AF and several risk scores have been developed to predict the risk of ischemic stroke and guide the decision to treat them with anticoagulants. The $CHADS_2$ risk score is the simplest score and assigns points to the presence of congestive heart failure, hypertension, age ≥75, diabetes, and stroke (1). To better identify patients that are truly at low risk, the CHA_2DS_2-VASc risk score was developed that also included vascular disease, age between 65 and 74 years, and sex (2). Both the U.S. and European guidelines now recommend use of the CHA_2DS_2-VASc score for risk stratification.

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The recent European Society of Cardiology guideline recommends treating patients with vitamin K antagonists or novel oral anticoagulants, depending on bleeding risk and patient preferences, when they have moderate (score = 1) or high (≥2) risk according to the CHA_2DS_2-VASc risk score (3). The U.S. guidelines, however, set the limit at 2 points or higher (4). Previous studies have reported that the $CHADS_2$ and the CHA_2DS_2-VASc risk scores have similar discriminating ability (C statistic ~0.6) (5–11). Recently a new clinically based risk score, the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study risk score, was developed and validated (12). This risk score uses factors incorporated in the $CHADS_2$ risk score, but added renal dysfunction. A broader range and increased weighting of age categories was used and the interaction of age and prior stroke was incorporated in the model, reflecting a high risk of stroke for patients with AF with a history of stroke regardless of age.

This study compares the predictive ability of the ATRIA risk score with the $CHADS_2$ and CHA_2DS_2-VASc risk scores in a large, independent, community-based cohort of patients with AF.

METHODS

STUDY POPULATION. Information for this study was obtained from the Clinical Practice Research Datalink (CPRD), which contains the computerized medical records of more than 10 million patients registered with general practitioners (GPs) in the United Kingdom. The data include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions, and major outcomes. About 50% of the practices in CPRD have been linked to other datasets in England, such as the Hospital Episode Statistics (HES). The HES includes records of inpatient hospitalizations, such as date of admission and discharge, diagnoses, and procedures performed. The current study used only practices that have been linked to HES.

The study population consisted of patients aged 18 years or older with a first AF diagnosis during the period of data collection (from January 1998 through January 2012). Patients with a record of rheumatic mitral stenosis and those with a prosthetic heart valve were excluded because of their altered stroke risk, resulting in a typical "nonvalvular" AF population. The index date was the date of first AF diagnosis. Patients were followed from the index date until the primary outcome occurred, end of data collection, or the date of the first warfarin prescription, whichever date came earliest. The primary outcome was ischemic stroke recorded either in CPRD (according to Read coding), HES (according to International Classification of Disease-10 codes), or both to ensure completeness of information.

UNIVARIABLE AND MULTIVARIABLE ANALYSIS OF RISK FACTORS. Multiple potential risk factors for ischemic stroke were identified: age, body mass index, smoking status, number of visits to the GP, ethnicity, socioeconomic status, history of congestive heart failure, hypertension, diabetes mellitus, vascular disease (i.e., angina pectoris, myocardial infarction), prior stroke or transient ischemic attack (TIA), deep venous thrombosis or pulmonary embolism, major bleeding event, proteinuria, and renal dysfunction. Diagnostic codes were extracted from both HES (International Classification of Disease-10 codes) (Online Table 1) and CPRD (Read codes) (Online Appendix 1).

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For renal failure and proteinuria, laboratory test records were used in addition to diagnostic codes. Renal dysfunction was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 or a diagnosis of renal failure (13). Patients that did not have a laboratory value or a diagnostic code for renal failure or proteinuria were assumed to have normal values. All risk factors were assessed at baseline. Stepwise backward selection of risk factors was used with a significance level for removal from the model of 0.20. An indicator variable for "missingness" was included in the model. With the risk factors left in the model we tested the presence of statistical interaction with age and sex. The interaction term was considered strong enough for inclusion in the final model when found statistically significant after Bonferroni adjustment of the significance level. When interaction tests are done for individual combinations of predictors, a stringent p value should be used (14).

COMPARING RISK SCORES. The 1-year risk of ischemic stroke was calculated for each patient according to the ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores. The risk factors and weightings that were considered for each risk score are listed in Tables 1 and 2. The C statistic, a measure of the area under the receiver operating characteristic curve, was calculated to determine the predictive ability of each risk score to discriminate between patients who developed the outcome and those that did not. We presented 95% confidence interval (CI) using the jackknife method (15). A C statistic of ≥0.5 indicates that the risk score performs better than chance. The net reclassification index (NRI) was also calculated to assess the proportion of person-years correctly up-plus down-reclassified when using the ATRIA risk score instead of the conventional CHA_2DS_2-VASc and $CHADS_2$ risk scores (15,16). Threshold rates of ischemic stroke of 1% and 2% per year were used to discriminate between low-, moderate-, and high-risk categories. These limits were chosen on the basis of a published decision model that investigated the tipping point at which the benefits and risks of taking anticoagulants were balanced (17). All statistical analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

TABLE 1 Overview of Used Risk Scores: Risk Factors Used in ATRIA Risk Score

Risk Factor	Points Without Prior Stroke	Points With Prior Stroke
Age, yrs		
≥85	6	9
75–84	5	7
65–74	3	7
<65	0	8
Female	1	1
Diabetes mellitus	1	1
CHF	1	1
Hypertension	1	1
Proteinuria	1	1
eGFR <45 or ESRD	1	1

ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease.

TABLE 2 Overview of Used Risk Scores: Risk Factors Used in CHA_2DS_2-VASc Risk Score and $CHADS_2$ Risk Score

	Score
CHA_2DS_2-VASc Risk Score	
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75 yrs	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65–74 yrs	1
Sex category (female/male)	1
$CHADS_2$	
Congestive heart failure	1
Hypertension	1
Age ≥75 yrs	1
Diabetes mellitus	1
History of stroke/TIA	2

$CHADS_2$ = congestive heart failure, hypertension, age ≥75, diabetes, and stroke; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex; LV = left ventricular; TE = thromboembolic event; TIA = transient ischemic attack.

SENSITIVITY ANALYSIS. Several sensitivity analyses were carried out to test the robustness of our findings. In both CPRD and HES, stroke events are in some cases not specified as ischemic or hemorrhagic and registered as "stroke unspecified." These events were assumed in our analysis to be ischemic strokes. In a sensitivity analysis we excluded these unspecified events to assess the impact on our findings. In 29% of patients there was missing information on renal function. We assessed if the performance of the ATRIA score would change without including information on renal dysfunction. Friberg et al. (18) recently recommended excluding events that occur immediately following the initial diagnosis of AF (the "blanking period") to prevent an overestimation of the stroke risk associated with AF. Therefore, we performed a sensitivity analysis in which a 4-week blanking period was included to compensate for an initial high stroke rate. We observed lower stroke rates in the second half of follow-up: 3.5% per year versus 2.8% per year. As a sensitivity analysis, we

TABLE 3 Baseline Characteristics of the Study Population

Risk Factor	Level	Patients With AF (n = 60,594)	%
Follow-up, yrs	Mean	2.81	
	Median	0.74	
	Percentiles 5th-95th	0.02–8.13	
	Interquartile range	0.13–3.13	
Age, yrs	Mean	74.4	
Age category, yrs	<65	11,742	19.4
	65–74	14,923	24.6
	75–84	21,637	35.7
	≥85	12,292	20.3
Sex	Male	31,088	51.3
BMI, kg/m^2	Underweight	2,736	4.5
	Normal weight	15,722	25.9
	Overweight	19,746	32.6
	Obese	13,491	22.3
	Not recorded	8,899	14.7
GP visits	≥20	40,381	66.6
Smoking	Nonsmoking	30,298	50.0
	Current-smoking	9,421	15.6
	Ex-smoking	17,272	28.5
	Not recorded	3,603	6.0
Diabetes mellitus		7,397	12.2
Congestive heart failure		10,571	17.5
Hypertension		33,026	54.6
Stroke/TIA		8,916	14.7
Vascular disease		18,636	30.8
Proteinuria		1,756	2.9
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)		16,990	28.0

AF = atrial fibrillation; BMI = body mass index; GP = general practitioner; other abbreviations as in Tables 1 and 2.

repeated our comparison of the 3 stroke risk schemes limiting the study population to those in years 2005 to 2012. Finally, the risk scores were also tested when the point score cutoffs were optimized to fit the 1% and 2% thresholds in the current dataset for the $CHADS_2$ (0, 1, 2 to 6 points), CHA_2DS_2-VASc (0 to 1, 2, 3 to 9), and ATRIA (0 to 2, 3 to 5, 6 to 15) risk scores.

RESULTS

The study population included 60,594 patients with AF untreated with warfarin. Approximately 3,000 patients per year were included in 1998 to 2000, and 4,000 to 5,000 patients per year were included from 2001 onward. The mean follow-up time (from the date of the AF diagnosis up to start of warfarin or end of data collection) was 2.1 years and the mean age at entry to the cohort was 74.4. Table 3 shows commonly recorded diagnoses, including hypertension (54.6%), vascular diseases (30.8%), and renal dysfunction (28.0%). A total of 3,751 ischemic strokes occurred during the follow-up period of 125,296 person-years, yielding an annualized rate of 2.99%.

The hazard ratios (HRs) of the clinical risk predictors from the univariable and multivariable analyses are shown in Table 4. Increasing age was a particularly strong risk factor among patients without a history of prior stroke or TIA. For example, among those patients, age 65 to 74 years conferred a HR of 2.87 (95% CI: 2.40 to 3.42) compared with younger patients. The effect of age was muted among patients who had had a prior stroke or TIA. Even relatively young patients with a history of prior stroke or TIA were at high risk for a subsequent stroke. The interaction between age and prior stroke was statistically significant ($p < 0.001$). Several other significant risk factors were confirmed. Small multivariable associations were found including female sex (HR: 1.23; 95% CI: 1.14 to 1.32), hypertension (HR: 1.14; 95% CI: 1.06 to 1.22), and diabetes mellitus (HR: 1.24; 95% CI: 1.12 to 1.37). Vascular disease, major bleed, renal dysfunction (estimated glomerular filtration rate <60 ml/min/1.73 m^2), and congestive heart failure were associated with a higher risk in the univariate but not multivariate analysis.

The **Central Illustration** shows the proportion of patients that were classified at low, moderate, or high risk for ischemic stroke according to each of the different risk scores. The ATRIA risk score classified 49.0% of patients into the high-risk category and 40.0% as low, whereas the CHA_2DS_2-VASc risk score classified 82.6% as high and 6.6% as low risk.

The C statistics for the continuous risk scores were 0.70 (95% CI: 0.69 to 0.71) for the ATRIA risk score, 0.68 (95% CI: 0.67 to 0.69) for the $CHADS_2$, and 0.68 (95% CI: 0.67 to 0.69) for the CHA_2DS_2-VASc risk score. The categorical risk scores, using the published low/moderate/high risk cutoffs (Table 5) resulted in C statistics of 0.66 (95% CI: 0.66 to 0.67) for the ATRIA, 0.65 (95% CI: 0.64 to 0.66) for the $CHADS_2$, and 0.59 (95% CI: 0.59 to 0.60) for the CHA_2DS_2-VASc risk score.

Table 5 shows ischemic stroke event rates stratified by the different risk scores. The event rates for the moderate- and high-risk categories for CHA_2DS_2-VASc were lower than those of the ATRIA and $CHADS_2$ risk scores. The event rate in the moderate-risk category of the CHA_2DS_2-VASc risk score (1 point) was 0.78 per 100 person-years. When we excluded individuals whose only risk factor was being female, the annual rate of stroke was 0.36%.

The NRI was 0.137 (95% CI: 0.120 to 0.153) or 0.233 (95% CI: 0.219 to 0.248) when using the ATRIA versus the $CHADS_2$ or CHA_2DS_2-VASc risk scores, respectively. These improvements resulted mainly from downward reclassification from the $CHADS_2$ score and entirely from downward reclassification from the

TABLE 4 Risk Factors for Ischemic Stroke in Patients With AF

Risk Factor	Level	Ischemic Stroke		
		Rate Per 100 Person-Years	HR (95% CI) Crude	HR (95% CI) Adjusted*
Age × prior stroke/TIA, yrs	<65, stroke	6.63	10.63 (8.0–14.15)	10.58 (7.93–14.12)
	65–74, stroke	8.01	12.67 (10.63–15.53)	12.37 (10.04–15.23)
	75–84, stroke	8.77	13.99 (11.74–16.66)	13.10 (10.91–15.73)
	≥85, stroke	10.56	16.46 (13.73–19.73)	14.94 (12.33–18.09)
	<65, no stroke	0.57	Reference	Reference
	65–74, no stroke	1.75	2.96 (2.48–3.52)	2.87 (2.40–3.42)
	75–84, no stroke	3.05	5.14 (4.37–6.03)	4.80 (4.07–5.66)
	≥85, no stroke	4.46	7.30 (6.19–8.62)	6.55 (5.50–7.78)
Sex	Male	2.37	Reference	Reference
	Female	3.59	1.54 (1.43–1.64)	1.23 (1.14–1.32)
BMI, kg/m^2	Underweight	3.82	1.22 (1.05–1.42)	1.08 (0.93–1.25)
	Normal weight	2.99	Reference	Reference
	Overweight	2.94	0.97 (0.89–1.06)	1.02 (0.94–1.11)
	Obese	2.48	0.79 (0.72–0.88)	0.92 (0.83–1.03)
	Not recorded	3.47	1 .19 (1.08–1.30)	1.17 (1.05–1.29)
GP visits	<20	2.43	Reference	Reference
	≥20	3.40	1.29 (1.21–1.38)	0.92 (0.85–0.99)
Smoking	Nonsmoking	0.78	Reference	Reference
	Current-smoking	10.67	0.84 (0.76–0.93)	1.08 (0.97–1.19)
	Ex-smoking	2.94	0.90 (0.83–0.97)	0.98 (0.90–1.06)
	Not recorded	2.97	1.01 (0.9–1.14)	0.94 (0.82–1.08)
Antiplatelet agents		3.60	1.43 (1.34–1.52)	0.97 (0.90–1.04)
Diabetes mellitus		4.01	1.30 (1.18–1.43)	1.24 (1.12–1.37)
Congestive heart failure		4.25	1.41 (1.30–1.53)	1.03 (0.94–1.12)
Hypertension		3.70	1.48 (1.38–1.58)	1.14 (1.06–1.22)
Vascular disease		3.54	1.23 (1.15–1.31)	0.98 (0.91–1.06)
Proteinuria		3.75	1.14 (0.93–1.39)	0.98 (0.80–1.21)
Renal dysfunction		4.30	1.53 (1.42–1.63)	1.06 (0.98–1.14)
Major bleed		3.61	1.17 (1.06–1.30)	0.95 (0.86–1.05)
DVT/PE		3.74	1.18 (0.89–1.56)	0.82 (0.62–1.09)

*Adjusted by age, sex, diabetes, hypertension, renal dysfunction, social economic status, smoking status, stroke, vascular disease, and usage of antiplatelet agents at baseline.
CI = confidence interval; DVT = deep venous thrombosis; HR = hazard ratio; PE = pulmonary embolism; other abbreviations as in Tables 2 and 3.

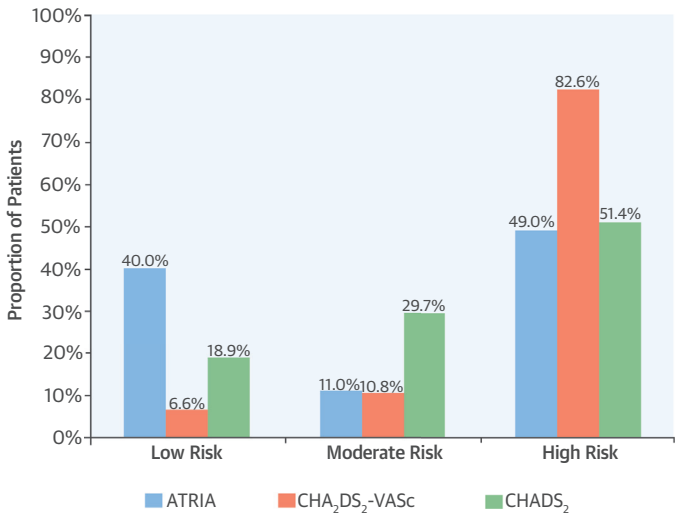
CHA_2DS_2-VASc score. The performance of the ATRIA risk score did not change significantly when renal dysfunction was removed from the risk score. When "unspecified" strokes were excluded, or when a blanking period of 4 weeks was used, the overall stroke rates decreased but the relative performance of the ATRIA risk score persisted. In addition, we restricted the analysis to the second half of the study (see the Methods section) including 44,784 patients and 2,362 events. The C statistic and NRIs did not differ from the main analysis. The results of these sensitivity analyses can be found in Online Table 2.

The risk scores were also tested when the point score cutoffs were optimized to fit the 1% and 2% thresholds in the current dataset for the $CHADS_2$ (0, 1, 2 to 6 points), CHA_2DS_2-VASc (0 to 1, 2, 3 to 9), and ATRIA (0 to 2, 3 to 5, 6 to 15) risk scores. Using these optimized cutpoints, the C statistic for the 3-category $CHADS_2$ and CHA_2DS_2-VASc risk score improved to 0.65 (95% CI: 0.64 to 0.66) and 0.63 (95% CI: 0.62 to 0.64), respectively, whereas the C statistic for the ATRIA score did not change. The NRI for ATRIA decreased to 0.033 (95% CI: 0.021 to 0.046) compared with the $CHADS_2$ risk score and 0.084 (95% CI: 0.076 to 0.093) compared with the CHA_2DS_2-VASc risk score.

DISCUSSION

This study found that the ATRIA risk score performed better than the $CHADS_2$ and CHA_2DS_2-VASc risk scores with a higher C statistic and positive NRI. This pattern persisted in sensitivity analyses where we restricted the analysis to the more recent half of the cohort's follow-up period, when we excluded "unspecified" strokes as outcome events and when we excluded renal dysfunction as a predictor. The improvement in risk classification resulted mainly from downward

CENTRAL ILLUSTRATION **Comparing Risk Scores for the Prediction of Stroke in Atrial Fibrillation: ATRIA, $CHADS_2$, and CHA_2DS_2-VASc Risk Scores**



van den Ham, H.A. et al. J Am Coll Cardiol. 2015; 66(17):1851–9.

Percentages of patients classified into low, moderate, and high risk according to the ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores. ATRIA = Anticoagulation and Risk Factors in Atrial Fibrillation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75, diabetes, and stroke; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age between 65-74, and female sex.

reclassification. Patients with a CHA_2DS_2-VASc risk score of 1 seem to have an absolute risk of <1%. As a consequence, applying the CHA_2DS_2-VASc risk score in a community-based population, such as the CPRD, might lead to overtreatment of very low stroke risk patients.

The C statistics of all risk scores showed moderate discriminative ability. However, the C statistic has proved to be inelastic and shows little improvement when important risk factors are added to the prediction model. Examples of this (change of 0.01 to 0.02 in C statistic) include individual well-known and proved risk factors, such as systolic blood pressure, smoking, and total cholesterol in predicting coronary heart disease (19). The NRI is a measure that attempts to quantify the added predictive ability of a new marker by assessing the proportions of patients (or patient-years) that are correctly reclassified into broad risk categories when using a different model. These categories are relevant to treatment decisions. Our findings were consistent with the original report of the ATRIA stroke risk score (12).

The CHA_2DS_2-VASC risk score was developed to identify those patients who are truly at low risk (2). As a consequence, fewer patients are assigned to the low-risk category with the CHA_2DS_2-VASC risk score than when using ATRIA or $CHADS_2$ risk scores. There is debate about the threshold at which patients should be treated. A simulation study of Eckman et al.

TABLE 5 **Ischemic Stroke Event Rates Stratified by the Sum of Points for ATRIA, $CHADS_2$, and CHA_2DS_2-VASc Risk Scores**

	ATRIA				$CHADS_2$				CHA_2DS_2-VASc			
Points	Events	PY × 1,000	Rate per 100-PY	OR (95% CI)	Events	PY × 1,000	Rate per 100-PY	OR (95% CI)	Events	PY × 1,000	Rate per 100-PY	OR (95% CI)
0	51	12.8	0.40	Reference	250	32.1	0.78	Reference	45	11.8	0.38	Reference
1	70	11.6	0.60		933	40.1	2.33		130	16.8	0.78	1.99 (1.42–2.80)
2	31	4.2	0.73		1,117	31.7	3.52	2.89 (2.51–3.32)	412	21.5	1.92	8.96 (6.68–12.02)
3	93	7.1	1.31		661	12.4	5.34		766	27.0	2.84	
4	194	10.3	1.89		598	6.7	8.98	5.71 (5.01–6.51)	896	24.2	3.70	
5	251	12.6	1.99		162	2.1	7.90		702	13.8	5.08	
6	338	14.4	2.35	1.97 (1.73–2.24)	30	0.3	11.50		472	6.7	7.09	
7	531	14.9	3.57	4.17 (3.84–4.54)					235	2.6	8.98	
8	687	14.0	4.91						79	0.9	9.01	
9	642	11.1	5.80						14	0.1	15.49	
10	415	7.3	5.69									
11	272	3.3	8.26									
12	127	1.3	9.47									
13	42	0.4	10.89									
14	7	0.0	14.26									
15	0	0.0	0.00									
All	3,751	125.3	2.99									

Black lines identify threshold for low-, moderate-, and high-risk categories for the 3 stroke risk point scores using the published cutpoints.
OR = odds ratio; PY = person-years; other abbreviations as in Tables 1, 2, and 4.

(17) concluded that the threshold for warfarin treatment should be at a stroke rate of 1.7% per year. In the CPRD population, the event rate in the CHA_2DS_2-VASc moderate-risk category was about one-half of that. Preferably, patients with these low stroke risks should not be treated with vitamin K antagonists. The most recent European Society of Cardiology guideline does not consider female sex as a standalone risk factor. Even if we exclude individuals whose only risk factor was being female, the annual rate of stroke for patients with a CHA_2DS_2-VASC risk score of 1 was very low at 0.36%. The same paper by Eckman et al. showed that the threshold for treatment with a new oral anticoagulant is 0.9% per year, because these agents seem to pose a lower risk of intracranial bleeding (20). But, even this risk threshold is higher than the stroke rate observed for patients with a CHA_2DS_2-VASC risk score of 1.

Because the risk category thresholds that we used were fixed at 1% and 2% per year, the proportions of patients accurately classified varies with the reported stroke rates in different cohorts. The ATRIA risk score was developed on a cohort with an overall stroke rate of 2% per year, whereas the CPRD AF cohort rate was 3% per year. The fit of the $CHADS_2$ and CHA_2DS_2-VASc risk scores was improved by adjusting the point score thresholds for low and high risk. With such optimized thresholds the NRI advantage of the ATRIA score diminished but was still positive. In case of any new evidence on different cutoff points for the discrimination between low-, moderate-, and high-risk groups, the NRI will be affected. For example, if the threshold is set higher (2% and 3%), ATRIA performs better.

Recently, 2 studies reported that the CHA_2DS_2-VASc score was superior to the ATRIA score in classifying low-risk patients in a Danish national cohort and a Taiwanese national cohort of patients with AF (21,22). The absolute stroke rates reported for these cohorts were much higher than those that we observed for the U.K. CPRD AF cohort, and this likely explains much of the difference in results. For ATRIA point scores of 0 to 5 (i.e., the original ATRIA low-risk category) the absolute stroke risk was 1.18% per year for the U.K. CPRD cohort that we studied, 3.22% per year for the Danish cohort, and 2.95% for the Taiwanese cohort. This highlights the variation in stroke rate among different cohorts, but also differences in methods used for detecting stroke cases in these electronic health care databases. As a point of reference, previous studies of the Danish cohort (8) reported stroke rates substantially higher than a similar Swedish national AF cohort (6). For patients in CHA_2DS_2-VASc score strata of 0 to 3 points the stroke rates observed in the Swedish AF cohort and the U.K. CPRD cohort are in close agreement. Friberg et al. (18) studied the impact of variation in the definition of stroke in the Swedish cohort and found that for patients with AF and a CHA_2DS_2-VASc score of 1 the stroke rate is lower than previously reported. This was attributed to the inclusion or exclusion of TIAs and pulmonary embolism, including patients with a secondary diagnosis of stroke, and considering an initial blanking period (18,23). In the current study we demonstrated that the blanking period did change the absolute stroke rate, but did not affect the relative performance of the risk scores. This may be due to the fact that the AF diagnosis in CPRD is recorded by the GP and not in the hospital as is done in the Swedish database. A diagnosis in the hospital can be a secondary AF diagnosis when a patient seeks medical attention because of an unrelated acute disease, whereas the GP often records a true incident AF case. The difference in stroke rate is probably mostly explained by the difference in definition and ascertainment of stroke rather than by true differences in stroke rates, although this issue needs further study.

There have been numerous studies that identified independent risk factors for ischemic stroke (24). We confirmed that female sex, increasing age, prior stroke, hypertension, and diabetes are independent risk factors of ischemic stroke. We did not find any independent association of stroke with vascular disease, a distinctive component of the CHA_2DS_2-VASc score. We also did not find that congestive heart failure was a risk factor for stroke, a component of all 3 scores. This questions the value of inclusion of this risk factor in all risk scores. In the CPRD database we used a record of a clinical diagnosis for heart failure. This was not supported with echocardiographic evidence, which might lead to misclassification and affect the reliability of this risk factor (25). These findings are consistent with results from the Swedish AF cohort in which independent risk factors were studied (6).

Several studies have investigated the importance of renal failure and proteinuria in relation with ischemic stroke (26–28). It is likely that this is an important risk factor for ischemic stroke, considering that this is closely related to the pathophysiology of heart failure, hypertension, diabetes mellitus, and vascular disease. In the current study we did not find an association of renal dysfunction and proteinuria with ischemic stroke in the multivariable analysis. However, renal function and proteinuria are variables that are not regularly registered in the CPRD database and information may therefore be incomplete. Furthermore, because laboratory values are often reported in chronic kidney disease classes in the

database, we were not able to take the cutoff estimated glomerular filtration rate of <45 ml/min/1.73 m^2, as is used in the ATRIA risk score. Instead we used the cutoff at chronic kidney disease category 3 (<60 ml/min/1.73 m^2). Misclassified renal function might have reduced the performance of the ATRIA score to a small extent. The ATRIA score assigns a much higher weighting to increasing age categories. These weightings are consistent with our analysis of the CPRD AF cohort and likely contribute to the better performance of the ATRIA score.

STUDY LIMITATIONS. Accurate information on outcomes and risk factors is very important in developing prediction studies. Several studies have validated the accuracy and completeness of the data recorded in CPRD (29,30). Herrett et al. (29) found that for diagnoses in the disease group of the circulatory system, 85.3% of cases were confirmed. However, patients who do not regularly visit their physicians are less likely to have risk factors identified. Undetected risk factors lead to overestimates of stroke rates in low point score categories. Another limitation concerns the classification of type of stroke. Some events of stroke are recorded as unspecified stroke in CPRD. We assumed that these cases of stroke were ischemic, which could have resulted in a misclassification. However, in a sensitivity analysis, in which we only used the definite cases of ischemic stroke, there were no major differences in results.

CONCLUSIONS

The ATRIA, $CHADS_2$, and CHA_2DS_2-VASc risk scores for the prediction of ischemic stroke in AF perform modestly, with the ATRIA risk score performing best. This study underlines the fact that the performance of low-, moderate-, and high-risk point score thresholds is sensitive to absolute population stroke rates.

Wide differences in reported rates of ischemic strokes across cohorts need to be investigated to separate true variation in rates from variation caused by methodologic inconsistencies. Current guidelines advise to use anticoagulants in patients with CHA_2DS_2-VASc risk score of >0, but this cutoff and this risk score approach might be reconsidered because patients tend to have lower absolute risks in community-based populations. Better risk prediction can reduce overuse of anticoagulation in low stroke risk patients with AF, while at the same time guiding the appropriate use in patients at higher risk of stroke.

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REPRINT REQUESTS AND CORRESPONDENCE: Mrs. T.P. van Staa, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, the Netherlands. E-mail: T.P.vanStaa@uu.nl.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The decision to anticoagulate patients with atrial fibrillation should be based on their risk of ischemic stroke. The ATRIA, $CHADS_2$, and CHA_2DS_2VASc risk scores all perform modestly, with the ATRIA score slightly superior to the others in identifying low-risk patients who do not benefit from anticoagulation.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the extent to which incorporation of additional information, such as ethnicity, biochemical or genetic markers, and cardiovascular imaging findings, could enhance stroke risk stratification in patients with atrial fibrillation.

REFERENCES

1. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864–70.

2. Lip GYH, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–72.

3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385–413.

4. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;64:e1–76.

5. Fang MC, Go AS, Chang Y, et al. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol 2008;51:810–5.

6. Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort Study. Eur Heart J 2012;33:1500–10.

7. Stroke Risk in Atrial Fibrillation Working Group. Comparison of 12 risk stratification schemes to predict stroke in patients with nonvalvular atrial fibrillation. Stroke 2008;39:1901–10.

8. Olesen JB, Lip GYH, Hansen ML, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:dl24.

9. Poli D, Antonucci E, Grifoni E, et al. Stroke risk in atrial fibrillation patients on warfarin. Predictive ability of risk stratification schemes for primary

and secondary prevention. Thromb Haemost 2009;101:367–72.

10. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: incidence, prevalence, and prediction of stroke using the congestive heart failure, hypertension, age > 75, diabetes mellitus, and prior stroke or transient ischemic attack (CHADS2) risk stratification scheme. Am Heart J 2008;156:57–64.

11. Van Staa TP, Setakis E, Di Tanna G, et al. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost 2011;9:39–48.

12. Singer DE, Chang Y, Borowsky LH, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. J Am Heart Assoc 2013;2:e000250.

13. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.

14. Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Dordrecht, the Netherlands: Springer Science & Business Media, 2008.

15. Kremers WK. Concordance for Survival Time Data: Fixed and Time-Dependent Covariates and Possible Ties in Predictor and Time. Technical Report Series No. 80. Rochester, MN: The Mayo Foundation, 2007.

16. Pencina MJ, D'Agostino RB, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. Stat Med 2011;30:11–21.

17. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point. Circ Cardiovasc Qual Outcomes 2011;4:14–21.

18. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and a CHA2DS2-VASc score of 1. J Am Coll Cardiol 2015;65:225–32.

19. Cook NR. Assessing the incremental role of novel and emerging risk factors. Curr Cardiovasc Risk Rep 2010;4:112–9.

20. Gómez Outes A, Terleira Fernández A, Calvo-Rojas G, et al. Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. Thrombosis 2013;2013:640723.

21. Lip GYH, Nielsen P, Skjøth F, et al. The value of the European Society of Cardiology guidelines for refining stroke risk stratification in patients with atrial fibrillation categorised as low risk using the anticoagulation and risk factors in atrial fibrillation stroke score: a nationwide cohort study. Chest 2014;146:1337–46.

22. Chao T, Liu C, Wang K, et al. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk'Asian patients with atrial fibrillation. J Am Coll Cardiol 2014;64:1658–65.

23. Singer DE, Ezekowitz MD. Adding rigor to stroke risk prediction in atrial fibrillation. J Am Coll Cardiol 2015;65:233–5.

24. Pisters R, Lane DA, Marin F, et al. Stroke and thromboembolism in atrial fibrillation. Circ J 2012;76:2289–304.

25. Stroke Risk in Atrial Fibrillation Working Group. Independent predictors of stroke in patients with atrial fibrillation: a systematic review. Neurology 2007;69:546–54.

26. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009;119:1363–9.

27. Olesen JB, Lip GY, Kamper A, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med 2012;367:625–35.

28. Roldán V, Marin F, Manzano-Fernandez S, et al. Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation? Thromb Haemost 2013;109:956–60.

29. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol 2010;69:4–14.

30. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract 2010;60. e1288–36.

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APPENDIX For supplemental tables, please see the online version of this article.