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CLINICAL RESEARCH
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Comparison of the ATRIA, $CHADS_2$, and CHA_2DS_2-VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation

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Aims Better stroke risk prediction is needed to optimize the anticoagulation decision in atrial fibrillation (AF). The ATRIA stroke risk score (ATRIA) was developed and validated in two large California community AF cohorts. We compared the performance of the ATRIA, $CHADS_2$, and CHA_2DS_2-VASc scores in a national Swedish AF (SAF) cohort.

Methods and results We examined all Swedish patients hospitalized, or visiting a hospital-based outpatient clinic, with a diagnosis of AF from July 2005 through December 2010. Variables were determined from comprehensive national databases. Risk scores were assessed via C-index (C) and net reclassification improvement (NRI). The cohort included 152 153 AF patients not receiving warfarin. Overall, 11 053 acute ischaemic strokes were observed with mean rate 3.2%/year, higher than the 2%/year in the California cohorts. Using entire point scores, ATRIA had a good C of 0.708 (0.704–0.713), significantly better than $CHADS_2$ 0.690 (0.685–0.695) or CHA_2DS_2-VASc 0.694 (0.690–0.700). Using published cut-points for low/moderate/high risk, C deteriorated but ATRIA remained superior. Net reclassification improvement favoured ATRIA 0.16 (0.14–0.17) vs. $CHADS_2$ and 0.21 (0.20–0.23) vs. CHA_2DS_2-VASc. Net reclassification improvement decreased when cut-points were altered to better fit the cohort's stroke rates.

Conclusion In this SAF cohort, the ATRIA score predicted ischaemic stroke risk better than $CHADS_2$ or CHA_2DS_2-VASc. However, relative performance of the categorical scores varied by population stroke rates. Score cut-points may need to be optimized to better fit local population stroke rates.

Keywords Atrial fibrillation • Ischaemic stroke • Anticoagulation • ATRIA • $CHADS_2$ • CHA_2DS_2-VASc

Background

Atrial fibrillation (AF) is the most common significant heart arrhythmia, especially among the elderly. Atrial fibrillation is also the strongest, common risk factor for thromboembolism to the brain leading to acute ischaemic stroke.[1] Anticoagulant therapy reduces the risk of AF-associated thromboembolism by approximately two-thirds.[2] The major drawback of anticoagulant therapy is increased risk of bleeding.[3] Of special importance is the risk of intracranial haemorrhage with often devastating effects for the patient.[4] Accurate ischaemic stroke risk scores are needed to help physicians estimate the expected benefit of anticoagulants for patients with AF. In particular, the $CHADS_2$[5] and CHA_2DS_2-VASc[6] risk scores have been incorporated into various clinical guidelines to facilitate the anticoagulation decision. However, these scores have only a moderate ability to estimate the risk of ischaemic stroke.[7–9] The more recently developed ATRIA risk score performed better than the $CHADS_2$ and CHA_2DS_2-VASc in two large, community-based cohorts of

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patients with AF in California,[10] as well as in a large general practice database in the UK.[11] In the current study, we compare the three risk scores in a national cohort of AF patients assembled in Sweden, the Swedish AF (SAF) cohort, a source of patients used previously to validate the CHA_2DS_2-VASc score and repeatedly cited in guidelines (ESC guidelines).[1]

Methods

Scores

ATRIA is a recently proposed score aimed to predict risk of ischaemic stroke among patients with AF not receiving anticoagulant therapy.[10] ATRIA is based on the Anticoagulation and Risk Factors in Atrial Fibrillation cohort assembled from the Kaiser Permanente Northern California integrated healthcare system. All ATRIA cohort thromboembolic events were confirmed by clinician review of medical records. The major risk factors in the ATRIA score are patient age and prior ischaemic stroke; increasing age is weighted more heavily among those without prior stroke. Included but weighted less heavily in the ATRIA score are female sex, diabetes mellitus, heart failure, hypertension, and renal dysfunction defined as proteinuria, estimated glomerular filtration rate (eGFR) <45 mL/min per 1.73 m^2, or end-stage renal disease requiring renal replacement therapy (*Table 1*). $CHADS_2$ includes the variables heart failure, hypertension, age ≥ 75 years of age, diabetes mellitus, and previous ischaemic stroke or transient ischaemic attack (TIA), giving one point to each risk factor with the exception of previous ischaemic stroke (or TIA), which is assigned two points.[5] CHA_2DS_2-VASc adds female sex, previous vascular disease defined as previous myocardial infarction or peripheral arterial disease, and another age category between 65 and 74 years of age, to the $CHADS_2$ score. Each of these added variables is given one point, and age ≥ 75 years of age renders two points.[6] We did not include 'complex aortic plaque,' an imaging feature sometimes included in the CHA_2DS_2-VASc score.[1] Definitions of the variables are identical to the definitions given by Friberg *et al.* in the paper originally evaluating CHA_2DS_2-VASc in the Swedish cohort.[9] ATRIA was superior to $CHADS_2$ and CHA_2DS_2-VASc when the predictive ability was compared in the derivation cohort as well as in a separate validation cohort of patients with AF, the ATRIA-CVRN cohort, and in a general practice database in the United Kingdom.[10,11]

Table 1 ATRIA stroke risk model point scoring system

ATRIA stroke risk model		
Risk factor	**Points *without* prior stroke**	**Points *with* prior stroke**
Age ≥ 85	6	9
Age 75–84	5	7
Age 65–74	3	7
Age <65	0	8
Female	1	1
Diabetes mellitus	1	1
Chronic heart failure	1	1
Hypertension	1	1
Proteinuria[a]	1	1
eGFR <45 or ESRD	1	1

ATRIA indicates anticoagulation and risk factors in AF; age in years; eGFR, estimated glomerular filtration rate; ESDR, end-stage renal disease.
[a]All patients were given a value of 0 for the proteinuria risk factor in the present study.

Cohort

The SAF Cohort is based on information from two nationwide Swedish health care registers, the National Patient Register and the Prescribed Drug Register. The National Patient Register contains individual information on all hospitalizations and all visits to hospital outpatient clinics in Sweden since 1987 (http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish; 8 April 2015). The Prescribed Drug Register includes all dispensed prescriptions in Sweden since 1 July 2005, with information on the reason for the prescription when available.[12] Linkage between the registers is possible due to the personal identification number given to everyone living in Sweden and used in all the registers.

The cases of AF were identified in the National Patient Register. All patients with a diagnosis of AF between 1 July 2005 and 31 December 2010 were included. Atrial fibrillation was defined by the ICD-10 code I489 with or without any of the specifying sub codes A–F. Thus, both AF and atrial flutter were included. Patients who were taken care of in the primary care or in other open clinics not affiliated with a hospital during follow-up were not included. The register also provided information about co-morbidities assessed from 1987 and up to the date of index diagnosis of AF, defined by ICD-10 codes. Information about warfarin therapy was collected from the Prescribed Drug Register. During this time period, warfarin was the only available registered anticoagulant in Sweden. A minority of patients was using Marcoumar (phenprocoumon) or Sintrom (acenocumarol), which was available only on license. The current Swedish AF cohort is a continuation of the cohort reported previously but with two additional years of follow-up.[9]

The analyses were restricted to patients who did not use anticoagulant therapy during the follow-up period. Acute ischaemic stroke was the sole outcome event (ICD-10 code I63), excluding TIAs or other kind of thromboembolism sometimes considered in previous studies.[6,13,14] The outcome diagnosis, ischaemic stroke, was retrieved from the National Patient Register. A blanking period of 14 days after the index date was used to avoid including events that were registered twice or more due to transfer between hospitals, or reflecting events during the hospital stay possibly occurring prior to the AF diagnosis. The patients were censored at the date when the outcome event occurred, at the date of death, or at end of follow-up (31 December 2010).

The different variables included in ATRIA were re-evaluated in the SAF cohort. No information about eGFR or proteinuria was available for the cohort. Instead, we used the ICD-10 codes for renal failure (N17, N18 and N19), dialysis (DR016 and DR024), and renal transplantation (KAS00, KAS10 and KAS20) as a substitute for eGFR <45 mL/min per 1.73 m^2. All patients were given a value of 0 for the proteinuria risk factor. Only baseline variables were included in the analysis. Uni- and multivariable Cox-regressions were used for the evaluation. C-index[15] was used to quantify discrimination of the ATRIA score in the SAF cohort and was compared with C-index for the $CHADS_2$ and CHA_2DS_2-VASc scores in the same cohort. Both the full range of point scores and point scores divided into three ordered risk categories were analysed. In the first categorical analysis, we used cut-points for low, moderate, and high risk of ischaemic stroke, originally published for $CHADS_2$.[5] In the ATRIA score, low risk is defined as 0 up to and including 5 points, moderate risk as 6 points, and high risk as 7 or more points.[10] In $CHADS_2$, the corresponding values are 0–1, 2–3, and 4

or more points, and in CHA_2DS_2-VASc, the cut-points are 0, 1, and 2 or more points.[1,6] Secondly, we adjusted the cut-points of the scores to optimize their fit for an incidence of ischaemic stroke <1%/year (low risk), 1–2%/year (moderate risk), and >2%/year (high risk). Using the 1%/year and 2%/year cut-points for classifying patients as low, moderate, or high ischaemic stroke risk, we calculated the net reclassification improvement (NRI)[16,17] for the ATRIA compared with the $CHADS_2$ and CHA_2DS_2-VASc risk scores. Most simply, NRI assesses the reclassification of cohort patients into a lower or higher risk category when one risk scheme (here the ATRIA categorical score) is used instead of another risk scheme (here the $CHADS_2$ and CHA_2DS_2-VASc categorical scores). It is the sum of the net proportion of patients sustaining an event who are upclassified plus the net proportion of patients not sustaining an event who are downclassified. It has a range of −2 to +2. In the current paper, we use an extension of the original method adapted for prospective studies with different length of patient follow-up.[17] The analyses were first performed in the total cohort. We repeated the analyses on solely primary prevention patients, excluding those with a history of ischaemic stroke, and further assessed the scores using only fatal stroke as the outcome. In these subgroup analyses, we only used the published cut-points. While the primary focus of our analyses were comparisons between the ATRIA score and the $CHADS_2$ and CHA_2DS_2-VASc risk scores, we also provide in Supplementary material online C-index and NRI measures for comparisons with the R_2CHADS_2 and Framingham Heart Study risk scores, as well as the modification of the $CHADS_2$ used in the Canadian Cardiovascular Society AF guidelines.

The statistical analyses were conducted using SAS software 9.3 (SAS Institute, INC, Cary, NC, USA).

The study complied with the Declaration of Helsinki and the protocol was approved by the Stockholm local ethics committee (dnr 2010/852-3173 and 2012/456-32).

Results

The total number of patients with a diagnosis of AF during the defined time period was 307 351. After exclusion of patients with mitral stenosis or valvular surgery (13 039) or death within 14 days from the index date (10 343), 283 969 patients remained. Further exclusion of patients given warfarin therapy during the follow-up or having a diagnosis of ischaemic stroke within 2 weeks of inclusion, left 152 153 patients for analysis (*Figure 1*). These patients contributed 340 223 person-years of follow-up, with a mean follow-up time of 2.23 years (maximum 5.46 and median 2.06 years, with the 25th and 75th centile being 0.82–3.73 years, respectively). The total number of strokes observed during follow-up was 11 053 for an overall ischaemic stroke rate of 3.25%/year. *Table 2* shows baseline characteristics and incidence rates of ischaemic stroke during follow-up.

Variables included in the ATRIA score all showed univariable associations with the outcome of ischaemic stroke. These were particularly strong for age and prior ischaemic stroke. Patients with a history of prior stroke were at very high risk of subsequent stroke even if they were relatively young, a stroke by age interaction also observed in the original ATRIA analyses. In multivariable analysis, heart failure and renal failure were not significantly associated with ischaemic stroke (*Table 3*). However, these variables were still included in the final model following the original intention to validate the actual ATRIA risk score in the Swedish cohort.

Table 4 presents the total number of ischaemic stroke events as well as the incidence rate/100 person-years stratified by point score for the three risk schemes. The bold horizontal lines indicate the published cut-points for low/moderate/high-risk categories for the

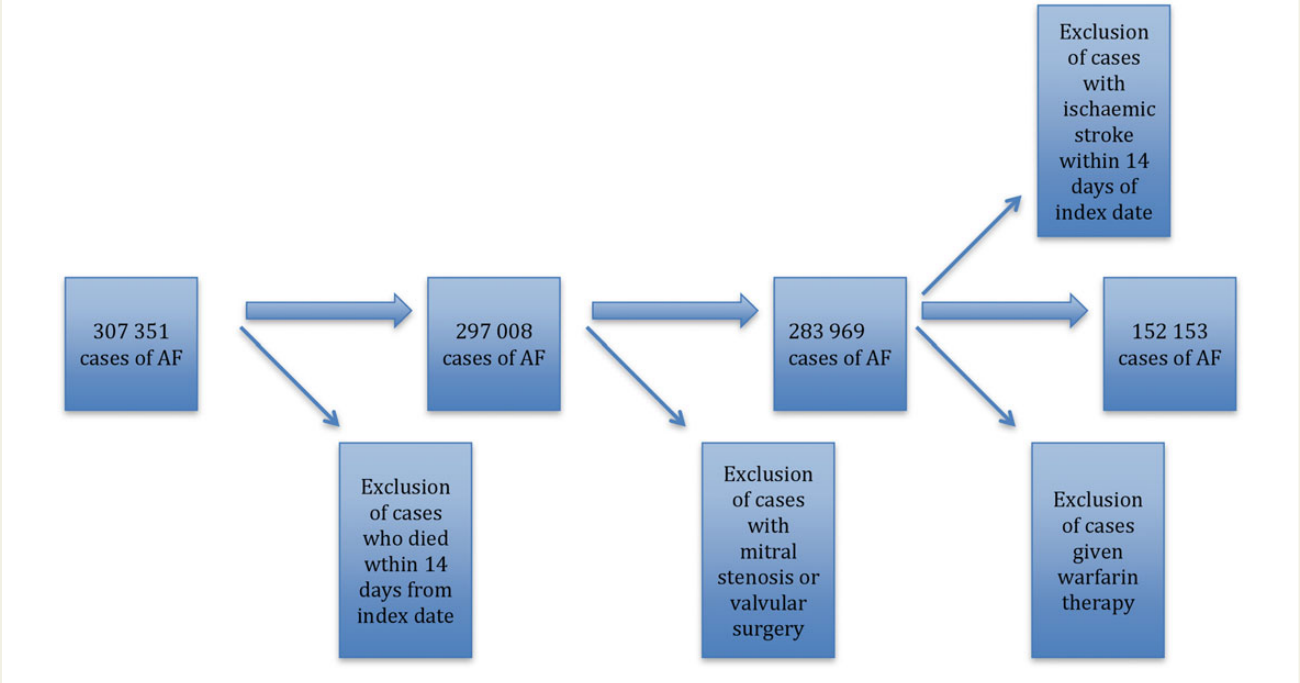

Figure 1 The study cohort.

Table 2 Baseline characteristics and rates of ischaemic stroke during follow-up

Variables	Patients (number)	Ischaemic stroke during follow-up (number)	Rate of ischaemic stroke/100 person-years
Prior stroke			
Yes	19 666	3196	9.69
No	132 487	7857	2.56
Age (years)			
<65	29 435	642	0.74
65–74	26 817	1487	2.14
75–84	47 792	4466	4.25
≥85	48 109	9144	11.64
Age, no prior stroke (years)			
<65	28 787	518	0.61
65–74	24 610	1090	1.68
75–84	40 125	3094	3.39
≥85	38 965	3155	4.81
Age, prior stroke (years)			
<65	648	124	8.11
65–74	2207	397	8.47
75–84	7667	1372	9.93
≥85	9144	1303	10.06
Sex			
Male	77 249	4578	2.57
Female	74 904	6475	4.00
Diabetes mellitus			
Yes	24 044	2029	4.24
No	128 109	9024	3.09
Heart failure			
Yes	43 239	3384	4.34
No	108 914	7669	2.92
Renal failure			
Yes	8325	516	4.16
No	143 828	10 537	3.21
Hypertension			
Yes	66 551	5816	4.22
No	85 602	5237	2.59
Total	152 153	11 053	3.25

three scores. Using the published cut-points, the ATRIA study distributed most patients as either low or high risk. In contrast, the CHA_2DS_2-VASc score assigned 82% of patients as high risk while the $CHADS_2$ score assigned only 15% as high risk (*Figure 2A*). When we optimized the scores' cut-points to fit the 1 and 2% per year rate thresholds (*Figure 2B*) the distribution of cases changed considerably and became much more alike.

Table 3 Univariable and multivariable analysis of risk factors included in ATRIA for the entire Swedish AF cohort

Variables	Univariable analysis hazard ratios with 95% confidence limits	Multivariable analysis hazard ratios with 95% confidence limits
Age, no prior stroke (years)		
<65	Reference	Reference
65–74	2.75 (2.47–3.05)	2.59 (2.33–2.88)
75–84	5.46 (4.97–5.99)	5.03 (4.57–5.52)
≥85	7.51 (6.84–8.24)	6.86 (6.23–7.54)
Age, prior stroke (years)		
<65	13.20 (10.85–16.05)	12.23 (10.05–14.89)
65–74	13.64 (11.97–15.55)	12.37 (10.84–14.11)
75–84	15.70 (14.18–17.37)	13.97 (12.60–15.48)
≥85	15.50 (14.00–17.17)	13.82 (12.45–15.34)
Sex		
Female/male	1.54 (1.48–1.60)	1.19 (1.14–1.24)
Diabetes mellitus	1.34 (1.28–1.41)	1.11 (1.06–1.17)
Heart failure	1.43 (1.37–1.48)	0.98 (0.94–1.02)
Renal failure	1.22 (1.11–1.33)	1.01 (0.93–1.11)
Hypertension	1.60 (1.54–1.66)	1.21 (1.16–1.26)

Using the entire point score range, the ATRIA score had a C-index of 0.708 (0.704–0.713), significantly better than the $CHADS_2$ score of 0.690 (0.685–0.695), or the CHA_2DS_2-VASc score of 0.694 (0.690–0.700). Using the categorical, published cut-points for low, moderate, and high ischaemic stroke risk, the C-index deteriorated for all scores but ATRIA and $CHADS_2$ were still superior to CHA_2DS_2-VASc, 0.668 (0.664–0.672), respectively, 0.663 (0.658–0.668) and 0.593 (0.591–0.595). However, the C-indices were quite similar when the cut-points in the categorical score were altered to better fit the Swedish cohort's ischaemic stroke rates. ATRIA then had a C-index of 0.633 (0.630–0.635), $CHADS_2$ 0.649 (0.646–0.653), and CHA_2DS_2-VASc 0.634 (0.631–0.637).

Using published cut-points for the categorical scores, NRI favoured ATRIA: 0.16 (0.14–0.17) vs. $CHADS_2$ and 0.21 (0.20–0.23) vs. CHA_2DS_2-VASc. These improvements resulted from predominant up-reclassification of the $CHADS_2$ score (with up-reclassification of events outweighing up-reclassification of non-events) and exclusive down-reclassification of the CHA_2DS_2-VASc score (with down-reclassification of non-events outweighing down-reclassification of events). Net reclassification improvement decreased to near zero when using the optimized cut-points, ATRIA −0.088 (−0.022 to 0.0041) vs. $CHADS_2$ and −0.00086 (−0.0094 to 0.0076) vs. CHA_2DS_2-VASc.

We evaluated the three risk scores in primary prevention patients in the SAF cohort. This sub-cohort consisted of 132 487 patients contributing 307 235 person-years of follow-up. All the C-indices

Table 4 Ischaemic stroke event rates by point score for ATRIA, $CHADS_2$, and CHA_2DS_2-VASc

Points	ATRIA				$CHADS_2$				CHA_2DS_2-VASc			
	Patients number (%)	Events	Person-years	Rate/100 person-years	Patients number (%)	Events	Person-years	Rate/100 person-years	Patients number (%)	Events	Person-years	Rate/100 person-years
0	12 938 (8.5)	164	39 878.12	0.4	29 659 (19.5)	641	87 719.83	0.7	12 266 (8.1)	142	37 839.13	0.4
1	10 868 (7.0)	200	32 175.58	0.6	38 209 (25.1)	2194	93 071.87	2.4	15 694 (10.3)	337	45 581.64	0.7
2	3729 (2.4)	96	10 249.86	0.9	37 525 (24.7)	2750	77 589.04	3.5	21 463 (14.1)	1028	54 540.93	1.9
3	7126 (4.7)	250	19 623.56	1.3	23 915 (15.7)	2405	44 252.45	5.4	29 199 (19.2)	1927	65 875.49	2.9
4	10 155 (6.7)	465	27 282.30	1.7	14 999 (9.8)	2032	25 514.56	8.0	29 479 (19.4)	2499	59 936.04	4.2
5	12 461 (8.2)	694	31 072.06	2.2	6387 (4.2)	840	10 014.83	8.4	21 367 (14.0)	2198	39 387.13	5.6
6	20 429 (13.4)	1473	46 316.00	3.2	1459 (1.0)	191	2060.78	9.3	13 755 (9.0)	1768	23 375.56	7.6
7	26 492 (17.4)	2242	53 322.03	4.2	–	–	–		6398 (4.2)	840	9974.05	8.4
8	22 304 (14.6)	2205	40 058.40	5.5	–	–	–		2166 (1.4)	270	3205.68	8.4
9	12 973 (8.5)	1515	21 497.45	7.0	–	–	–		366 (0.2)	44	507.72	8.7
10	6165 (4.0)	848	9661.04	8.8	–	–	–		–	–	–	–
11	4227 (2.8)	629	6139.73	10.2	–	–	–		–	–	–	–
12	1836 (1.2)	226	2450.04	9.2	–	–	–		–	–	–	–
13	409 (0.3)	42	464.61	9.0	–	–	–		–	–	–	–
14	37 (0.02)	4	32.56	12.3	–	–	–		–	–	–	–

Bold lines indicate thresholds for low-, moderate-, and high-risk categories for the three stroke risk scores, using published cut-points.
The full range score is limited to 14 points for ATRIA since all patients were given a value of 0 for the proteinuria risk factor.

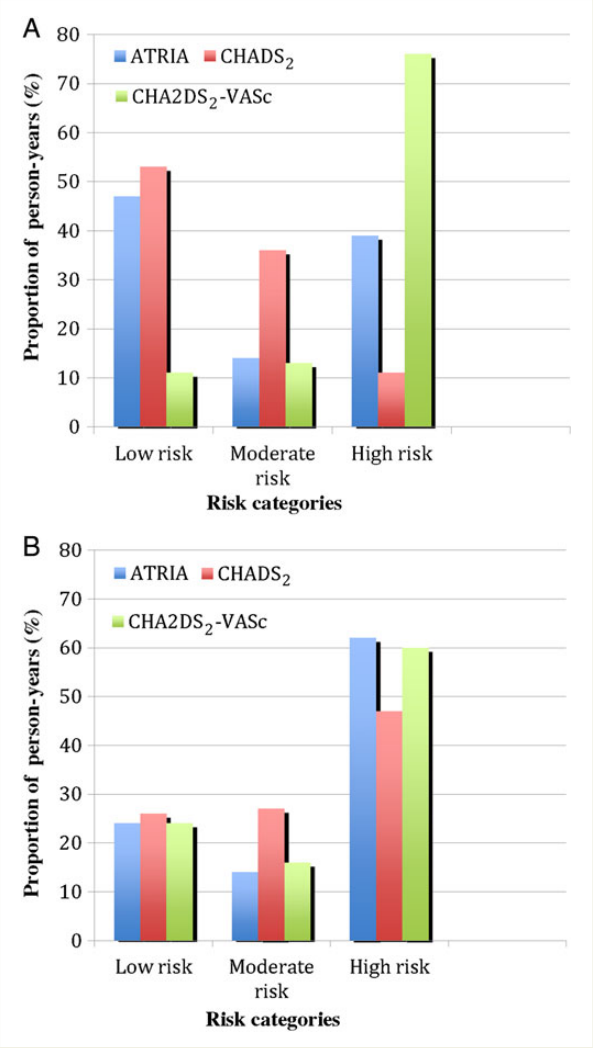

Figure 2 Distribution of cases according to risk categories, published cut-points (*A*) and optimized cut-points (*B*).

deteriorated but the full score ATRIA remained superior to $CHADS_2$ and CHA_2DS_2-VASc, for ATRIA 0.676 (0.671–0.682), for $CHADS_2$ 0.649 (0.644–0.655), and for CHA_2DS_2-VASc 0.667 (0.662–0.673). Net reclassification improvement for the categorical scores using published cut-points still favoured ATRIA, compared with $CHADS_2$, 0.19 (0.18–0.21), and compared with CHA_2DS_2-VASc, 0.14 (0.13–0.16).

Finally, we assessed the performance of the scores in predicting severe stroke events; with the 2289 fatal strokes classified as 'severe.' The analysis included 353 234 person-years of follow-up. The C-indices improved markedly for all three scores with the full-point ATRIA score performing best with a C-index of 0.766 (0.758–0.774), compared with $CHADS_2$, 0.738 (0.729–0.748), and with CHA_2DS_2-VASc, 0.749 (0.740–0.758). Net reclassification improvement gave even higher values for ATRIA, compared with $CHADS_2$, 0.24 (0.21–0.26) and compared with CHA_2DS_2-VASc, 0.32 (0.30–0.34) respectively, when using the published cut-points for the categorical scores.

Discussion

This validation study, based on a large, national cohort of Swedish AF patients, showed that the ATRIA stroke risk score predicted ischaemic stroke in patients with AF better than the established risk prediction scores $CHADS_2$ and CHA_2DS_2-VASc. Since all AF patients with a prior ischaemic stroke are at high risk for future stroke, accurate stroke risk prediction is probably more important for primary prevention patients where the anticoagulation decision is less clear. Although the performance of all three risk scores deteriorated somewhat in the primary prevention cohort, the ranking remained the same. In contrast, when applied to predicting the most important outcome, fatal stroke, our indicator of severe stroke, the scores performed better but again the ATRIA score was the most accurate. These findings validate those found in the California AF cohorts[10] and in a cohort of patients with AF in the UK.[11] Of note, the Swedish AF cohort used in the current study was based on the same cohort as that used as an original validation cohort for the CHA_2DS_2-VASc score and cited in the ESC guidelines.[9]

The variables included in the ATRIA, $CHADS_2$ and CHA_2DS_2-VASc scores overlap substantially. The superior performance of the ATRIA score, particularly when comparing the complete range scores, largely reflects inclusion of more age categories, and a more complicated but likely more accurate weighting system based on formal statistical modelling. The ATRIA score is more complicated than the $CHADS_2$ and CHA_2DS_2-VASc scores but should pose no problem for computer or smart device applications for clinical practice. The ATRIA score assigns particularly high weights to age categories and prior ischaemic stroke, since these two features account for a large fraction of stroke risk prediction. In contrast, both the $CHADS_2$ and CHA_2DS_2-VASc scores were based on informal assessment of preceding studies, and not on formal statistical modelling, and their point scores favoured simplicity over statistical accuracy. One consequence of this approach is that patients with a given $CHADS_2$ or CHA_2DS_2-VASc score may face substantially different stroke risks. This is a particular concern for patients at the low-risk threshold of the CHA_2DS_2-VASc score where a score of 1 point conferred by, e.g. hypertension, likely corresponds to a much lower stroke risk than the score of 1 point conferred by age 65–74 years.[18,19] The value of CHA_2DS_2-VASc 1 point as the threshold for anticoagulant therapy has recently been questioned.[18,19]

For the most part, AF stroke risk scores are applied clinically as categorical scores: low, moderate, and high risk. It is not certain what absolute stroke risk best corresponds to low, moderate, and high risk. Yet, guidelines implicitly and decision modelling explicitly identify 1 and 2% per year thresholds.[1,20] In the ESC guidelines, low stroke risk is restricted to patients with a CHA_2DS_2-VASc score of 0. Long-term anticoagulant therapy is recommended for patients with AF whose CHA_2DS_2-VASc score is 1 or greater. In our analysis, a CHA_2DS_2-VASc score of 1 corresponded to an ischaemic stroke rate of 0.7% per year. Assuming a two-thirds risk reduction by use of anticoagulants, the number needed to treat (for 1 year) to prevent 1 stroke is >200, likely conferring little net clinical benefit after bleed risk is considered. Using the original published point score thresholds, the CHA_2DS_2-VASc score had a markedly inferior C-index. However, when we optimized the point score cut-offs for the three

risk schemes, the C-indices converged and the NRI values moved towards zero. This finding highlights the fact that point scores may correspond to different absolute stroke risks in different cohorts of patients with AF. Methodological differences in assembling cohorts and identifying stroke outcomes likely explain much of these differences,[18,19] although there may be true differences in stroke risks across populations. Guideline writers need to carefully consider how well stroke risk cut-points apply to their targeted populations.

The current study has clear strengths. The Swedish population-based health care registers allow very large scale, high-quality epidemiological research. The National Patient Register covers all hospitalizations in Sweden and provides the foundation for long-term, comprehensive follow-up. Our ischaemic stroke outcome, in particular, is specific and has been validated against a national stroke registry based on clinical evaluation.[21]

Study limitations should also be acknowledged. Because the cohort is hospital based the absolute rates of stroke may be somewhat overestimated relative to community-based populations. This limitation applies to most studies based in national registers. Similarly, there may be undercoding of stroke risk factors, such as hypertension, in cohorts based on hospital diagnoses but this would apply across all stroke risk scores. eGFR and proteinuria assessments were not available. The substitute ICD-10 codes chosen as markers of renal failure may represent more severely ill patients. This would bias against the performance of the ATRIA score. However, this effect is likely not large since renal dysfunction is a relatively modest component of the ATRIA stroke risk score. We only analysed patients not taking anticoagulants. This is common practice in developing and assessing stroke risk scores for AF and is based on concern that anticoagulants may distort the relationship between risk factors and observed stroke rates. The exclusion may still introduce selection bias, although the effect on the comparison of the scores is expected to be minor. Finally, we note that a recent paper using a national Taiwan database reported a substantially higher C-index for the CHA_2DS_2-VASc over than the ATRIA score.[22] We find this result surprising given the inelasticity of C-index[23] and the fact that the ATRIA score includes all significant CHA_2DS_2-VASc risk factors plus an additional age category and a formally derived set of risk factor weights. The event rates reported for the Taiwanese cohort were 2.5 times higher than the rates we report for the Swedish AF cohort. To reconcile such disparate findings, there needs to be rigorous standardization of the analysis of national databases used to develop and assess AF stroke risk scores.[19]

Conclusion

Accurate ischaemic stroke risk scores are needed to help physicians estimate the expected benefit of anticoagulants for patients with AF. In the current analysis of the large, national Swedish AF cohort, we found that the ATRIA score performed better than the $CHADS_2$ or CHA_2DS_2-VASc scores that are currently incorporated into guidelines. We also demonstrated that categorical (low/moderate/high risk) score performance is sensitive to absolute stroke rates which appear to vary across cohorts, raising the possibility that cut-points on the multipoint scores may need to be adjusted for different target AF populations to achieve best ischaemic stroke preventive benefit from anticoagulant therapy.

Supplementary material

Supplementary Material is available at *European Heart Journal* online.

Authors' contributions

S.A., Y.C., M.B. performed statistical analysis; D.E.S. handled funding and supervision; S.A. acquired the data; D.E.S., S.A. conceived and designed the research; S.A., A.A., D.E.S. drafted the manuscript; D.E.S., M.B., A.S.G. made critical revision of the manuscript for key intellectual content.

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References

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;**31**:2369–2429.
2. Singer DE, Albers GW, Dalen JE, Fang MC, Go AS, Halperin JL, Lip GY, Manning WJ. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008;**133**(6 Suppl.):546S–592S.
3. Lip GY, Andreotti F, Fauchier L, Huber K, Hylek E, Knight E, Lane D, Levi M, Marín F, Palareti G, Kirchhof P. Bleeding risk assessment and management in atrial fibrillation patients: a position document from the European Heart Rhythm Association, endorsed by the European Society of Cardiology Working Group on Thrombosis. *Europace* 2011;**13**:723–746.
4. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007;**120**:700–705.
5. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. 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**:263–272.
7. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2008;**51**:810–815.
8. Keogh C, Wallace E, Dillon C, Dimitrov BD, Fahey T. Validation of the CHADS2 clinical prediction rule to predict ischaemic stroke. A systematic review and meta-analysis. *Thromb Haemost* 2011;**106**:528–538.
9. Friberg L, Rosenqvist M, Lip GY. 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**:1500–1510.
10. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. 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.
11. Van Den Ham HA, Klungel OH, Singer DE, Leufkens HGM, Van Staa TP. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke

in patients with atrial fibrillation in a national primary care database and the impact on treatment decisions. *J Am Coll Cardiol* 2015;**66**:1851–1859.
12. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, Persson I, Sundström A, Westerholm B, Rosén M. The new Swedish Prescribed Drug Register–opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**: 726–735.
13. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen AM, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;**342**:d124.
14. Poli D, Lip GY, Antonucci E, Grifoni E, Lane D. Stroke risk stratification in a 'real-world' elderly anticoagulated atrial fibrillation population. *J Cardiovasc Electrophysiol* 2011;**22**:25–30.
15. Kremers W. *Concordance for Survival Time Data: Fixed and Time-Dependent Covariates and Possible Ties in Predictor and Time*. Rochester, MN: Mayo Clinic; 2007.
16. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med* 2008;**27**:157–172.
17. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;**30**:11–21.
18. Friberg L, Skeppholm M, Terént A. Benefit of anticoagulation unlikely in patients with atrial fibrillation and CHAD2DS2-VASc score of 1. *J Am Coll Cardiol* 2015;**65**:225–232.
19. Singer DE, Ezekowitz MD. Adding rigor to stroke risk prediction in atrial fibrillation. *J Am Coll Cardiol* 2015;**65**:233–235.
20. Eckman MH, Singer DE, Rosand J, Greenberg SM. Moving the tipping point: the decision to anticoagulate patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes* 2011;**4**:14–21.
21. Asplund K, Hulter Åsberg K, Appelros P, Bjarne D, Eriksson M, Johansson A, Jonsson F, Norrving B, Stegmayr B, Terént A, Wallin S, Wester PO. The Riks-Stroke story: building a sustainable national register for quality assessment of stroke care. *Int J Stroke* 2011;**6**:99–108.
22. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Chen TJ, Lip GY, Chen SA. Using the CHA2DS2-VASc score for refining stroke risk stratification in 'low-risk' Asian patients with atrial fibrillation. *J Am Coll Cardiol* 2014;**64**:1658–1665.
23. Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem* 2008;**54**:17–23.