Comparison of Stroke Risk Stratification Scores for Atrial Fibrillation

Meytal Avgil Tsadok, PhD[a,c,*], Adi Berliner Senderey, MSc[a,c], Orna Reges, PhD[a,b,c], Morton Leibowitz, MD[a,c], Maya Leventer-Roberts, MD[a,c], Moshe Hoshen, PhD[a,c], and Moti Haim, MD[a,b,c]

Several stroke risk stratification scores have been developed to guide clinical decision-making in patients with nonvalvular atrial fibrillation (AF). The aim of this study was to compare the performance of the $CHADS_2$, CHA_2DS_2-VASc and R_2CHADS_2 risk scores to predict stroke. This retrospective cohort study was based on electronic medical records from Clalit Health Services (CHS), the largest payer provider healthcare organization in Israel. Data of CHS members with AF diagnosis between 2004 and 2015 were extracted. Demographic and co-morbidity data were used to calculate the 3 risk scores, and the performance of the scores to predict stroke were compared using area under the curve and net reclassification index. Of the 89,213 CHS members with AF, 52.3% were women and median age was 76 years. The proportions of patients at high risk were 66.2%, 86.7%, and 71.1% in the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2, respectively, with stroke incidence rates of 2.91, 2.35, and 2.80 per 100 person-years, respectively. Area under the curves for stroke prediction were 0.61 for both $CHADS_2$ and CHA_2DS_2-VASc and 0.59 for R_2CHADS_2. Net reclassification index analysis demonstrated a net improvement of 0.089 in the index when CHA_2DS_2-VASc was compared with $CHADS_2$ and a net reduction of 0.083 when R_2CHADS_2 was compared with $CHADS_2$. In conclusion, current stroke stratification scores have comparable but limited ability to predict stroke in patients with AF. Stroke prevention strategies may vary depending on the applied stratification. There is a need for a better stroke risk stratification score for patients with AF. **(Am J Cardiol 2019;123:1828−1834)**

Nonvalvular atrial fibrillation (AF) is associated with a substantial risk of ischemic stroke[1] depending on the presence of various risk factors. Different risk stratification scores have been developed to assess the risk of stroke in patients with AF, and to guide clinicians toward antithrombotic therapy. The $CHADS_2$ score is a tool that is clinically useful and simple to calculate. The CHA_2DS_2-VASc score incorporates additional risk factors beyond the $CHADS_2$ score, and is more likely to identify patients at low risk, who could be managed without antithrombotic therapy. The $CHADS_2$[2] and CHA_2DS_2-VASc[3] risk scores have been incorporated into various clinical guidelines, and their potential predictive value has been extended to nonstroke outcomes including the prediction of mortality.[4] Recent data suggest that incorporating renal dysfunction factors improves stroke prediction offered by the above mentioned risk scores, introducing the R_2CHADS_2 score, which assigns 2 points to creatinine clearance below 60 ml/min.[5] In this study, we compared the incidence of ischemic stroke and mortality according to the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 stratification scores in a large, population-based cohort of patients with AF, including analyses in a subpopulation of patients with AF who did not purchase anticoagulation therapy after AF diagnosis.

Methods

This retrospective cohort study was conducted using the Clalit Health Services' (CHS) electronic health record database. CHS is the largest payer provider healthcare organization in Israel, with more than 4.3 million insured residents, that provides care to >50% of the adult population over the age of 21 and to >60% of adults older than 65 years of age. The clinical and administrative database is kept in a central computerized data warehouse and includes demographic data and clinical diagnoses (based on hospital discharge diagnoses, as well as community primary care and specialist diagnoses). In addition, all laboratory data results, medical treatments, medical and surgical procedures, and medication prescription and purchasing information are recorded in the database.

The study population has been described previously.[6] Briefly, the cohort included adults 21 years or older with a new diagnosis of AF between the dates January 1, 2004 and December 31, 2015. Members with AF were identified

[a]Clalit Research Institute, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel; [b]Department of Health Systems Management, Ariel University, Israel; and [c]Cardiac Electrophysiology and Pacing, Cardiology Department, Soroka Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel. Manuscript received January 7, 2019; revised manuscript received and accepted February 26, 2019.

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*Corresponding author: Tel: 972-3-693-5916.

E-mail addresses: meytalts1@clalit.org.il; meytala@gmail.com (M. Avgil Tsadok).

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using the International Classification of Diseases, Ninth Revision diagnosis codes 427.3, 427.31, and 427.32. For the purpose of the present analysis, we did not distinguish between cases of atrial flutter (427.32) and AF (427.31). Codes from community clinics were cross validated with the accompanying text describing the diagnosis. Patients were considered to have AF only if the text associated with the diagnosis code supported a new diagnosis of AF.

The date at which the patient was first designated with any AF code was considered as the AF diagnosis index date. We excluded members who had an AF diagnosis before January 1, 2004 to ensure that only incident cases were included. We also excluded patients with a diagnosis of severe mitral or aortic valve disease, congenital heart disease, rheumatic heart disease, or those who underwent valve surgery before the index date. All patients had to be members of CHS for at least 1 year before the AF diagnosis.

$CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 scores were assigned to members with AF based on their clinical characteristics based on the presence of the relevant risk factors that comprise these scores before the AF diagnosis (index date). Codes that were used to define the scores' elements are described in Appendix 1. In all risk scores, a score of 0 was considered as low risk, a score of 1 was considered as moderate risk, and a score of 2 and more was considered as high risk.

Members with AF were considered to be using anticoagulation therapy if they purchased warfarin or new oral anticoagulants (new oral anticoagulant (NOACs): dabigatran, apixaban, or rivaroxaban) within 3 months after the index AF diagnosis date. This approach is akin to an intention-to-treat analysis in randomized, controlled trials.

The follow-up period began after the initial AF diagnosis and ended with stroke, death, or the end of the study period (December 31, 2015), whichever came first. The main outcome of interest was first hospital admission for stroke (International Classification of Diseases, Ninth Revision codes: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, and 436). To avoid capturing stroke events that were related to the index AF diagnosis, events of stroke outcomes were only considered if they occurred between 30 and 2,500 days after the index date. Data regarding transient ischemic attacks were not used for the purpose of analysis, as these diagnoses are less reliable and difficult to validate. Although the risk scores were not primarily designed to predict mortality, some studies have demonstrated their ability to predict death in both AF and non-AF populations, and therefore, we also included death as a secondary outcome. All-cause mortality data were obtained from the Israeli Ministry of Interior.

Distribution of risk strata (low, intermediate, and high risk) were described based on the 3 stratification scores: $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2. Descriptive statistics were used to compare demographic characteristics, co-morbidities, and pattern of oral anticoagulant (OAC) use of CHS members who were assigned to each risk strata in the 3 stratification scales. Continuous variables are presented as medians and interquartile ranges and dichotomous variables are presented as percentages. Incidence rates of ischemic stroke and mortality rates (30 to 2,500 days post index date) were calculated as the number of events per 100 person-years and are reported for each risk strata in the 3 stratification scales.

The measure of the area under the receiver operating characteristic curve (AUC) was calculated to determine the ability of each continuous risk score to discriminate between patients who developed stroke or died and those who did not. The 95% confidence interval was calculated using DeLong's method. We also calculated the net reclassification improvement (NRI) index to assess the relative proportion of outcome cases correctly reclassified when using the CHA_2DS_2-VASc or R_2CHADS_2 score compared with the $CHADS_2$ score. Hence, similar to Pencina et al,[7] we tested the net up and down movements of the change in classification of the patients' predicted outcomes as fractions of their true outcome groups based on the categorical risks scores.

As it has been previously suggested that stroke risk scores are best tested in a non anticoagulated population-based cohort,[8] as a sensitivity analysis, we repeated all analyses in a subpopulation of patients who did not purchase OACs within the first 3 months after the AF diagnosis (index date). Statistical analyses were conducted using the R language (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria) using the pROC package version 1.10.0 and the PredictABEL package version 1.2-23.

The study protocol was approved by CHS's Central Ethics Review Board.

Results

The cohort consisted of 89,213 patients with newly diagnosed AF between the years 2004 and 2015. Baseline characteristics of this study population are described in Table 1. The median age at date of AF diagnosis was 76.0 (interquartile range 65.0 to 83.0) years and women comprised 52.3% of the cohort. Common co-morbidities were hypertension, dyslipidemia, and diabetes. One-third of the AF cohort purchased any OAC treatment within 3 months after the AF diagnosis. The subpopulation of non-OAC users was comparable to the general CHS AF cohort in terms of baseline characteristics (Table 1).

The distribution of patients who were categorized into the low, intermediate, and high risk categories according to the different stratification scores are presented in Figure 1. The percentage of the high-risk group varied considerably across the risk scales: 66.2% according to the $CHADS_2$ score, 86.7% according to the CHA_2DS_2-VASc score, and 71.1% according to the R_2CHADS_2 score. Population characteristics based on the risk strata of the different scores are presented in Appendix 2. Overall, CHS members who were classified based on the CHA_2DS_2-VASc score were younger, had a lower burden of co-morbidities, and lower rates of OAC purchasing. In all risk scores, the overall rate of OAC purchasing increased.

During the follow-up period, we identified 5,752 events of stroke, with an overall incidence rate of 2.00 per 100 person-years (Table 2). In the subpopulation of patients who did not purchase OACs within the first 3 months after AF diagnosis, incidence of stroke rate per 100 person-years was 1.89. In all risk stratification scales, stroke

Table 1
Baseline demographic characteristics, clinical characteristics, and anticoagulation purchasing information of CHS members with atrial fibrillation

Variables	Clalit atrial fibrillation cohort (n = 89,213)	Non oral anticoagulation users (n = 60,001)
Age, [median (intra quartile range)], years	76.0 (65.0-83.0)	76.0 (64.0-84.0)
Women	46,640 (52.3%)	31,571 (52.6%)
Socioeconomic status		
Low	17,693 (20.1%)	12,460 (21.1%)
Medium	38,644 (43.9%)	25,996 (44.0%)
High	31,605 (35.9%)	20,643 (34.9%)
Missing	1,271 (1.4%)	902 (1.5%)
Sector		
Arab	10,055 (11.3%)	7,214 (12.0%)
Jew	79,155 (88.7%)	52,785 (88.0%)
Missing	3 (0.0%)	2 (0.0%)
Co-morbidities		
Hypertension	68,435 (76.7%)	43,884 (73.1%)
Diabetes mellitus	28,593 (32.1%)	17,914 (29.9%)
Dyslipidemia*	58,443 (65.5%)	37,392 (62.3%)
Acute myocardial infarction	22,547 (25.3%)	14,994 (25.0%)
Congestive heart failure	17,804 (20.0%)	11,670 (19.4%)
Previous stroke	15,459 (17.3%)	10,424 (17.4%)
Intracranial hemorrhage	1,091 (1.2%)	887 (1.5%)
Gastrointestinal bleeding	3,573 (4.0%)	2,881 (4.8%)
Peripheral vascular disease	4,815 (5.4%)	3,333 (5.6%)
Chronic kidney disease stage		
1	17,424 (20.0%)	12,759 (21.9%)
2	42,099 (48.4%)	26,695 (45.8%)
3	22,422 (25.8%)	14,920 (25.6%)
4	3,320 (3.8%)	2,576 (4.4%)
5	1,658 (1.9%)	1,364 (2.3%)
Missing	2,290 (2.6%)	1,687 (2.8%)
Anticoagulation purchasing within 3 months from index date		
Warfarin	25,386 (28.5%)	-
New oral anticoagulants	4,923 (5.5%)	-
Any oral anticoagulation	29,212 (32.7%)	-

* Dyslipidemia − defined based on diagnosis codes.

incidence increased with the increase of risk score. When compared with the $CHADS_2$ and R_2CHADS_2 scores, stroke incidence was lower when using the CHA_2DS_2-VASc score within each risk strata. In the high-risk category (≥2 points), the incident risk of stroke was 2.91, 2.35, and 2.80 in the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2, respectively.

In the entire Clalit AF cohort, 29,236 members died within the follow-up period, with a mortality rate of 9.66 per 100 person-years (Table 2). This rate was lower in the subpopulation of members who did not purchase OACs in the first 3 months after AF diagnosis, with an incidence rate of 6.85 per 100 person-years. In the 3 risk scores, mortality rates increased with increasing risk, with a more noticeable increment when shifting from the intermediate risk to high-risk strata. At each risk strata, mortality rates were lower when the risk strata based on the CHA_2DS_2-VASc score were compared with the $CHADS_2$ and R_2CHADS_2 scores. In the subpopulation of members who did not use OACs, trends were comparable to the entire population (Table 2).

For the stroke outcome, the 3 scores had a relatively similar predictive ability according to the AUC, ranging from 0.59 in the R_2CHADS_2 to 0.61 in both the $CHADS_2$ and CHA_2DS_2-VASc scores (Table 3). The results of the AUC analyses did not change substantially in the subpopulation of patients who did not purchase OACs within the 3 months after the AF diagnosis.

The AUC of the scores to predict mortality outcome was 0.58 according to the CHA_2DS_2-VASc score and 0.64 in both the $CHADS_2$ and R_2CHADS_2 scores. In the subpopulation of members who did not purchase OACs, the AUC values were 0.67, 0.60, and 0.66 in the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2, respectively (Table 3).

In the NRI analyses, switching from the $CHADS_2$ score to the CHA_2DS_2-VASc score improved the NRI index for stroke by 0.089, while the NRI of R_2CHADS_2 versus $CHADS_2$ score was negative (−0.083). Among the members who did not purchase OACs, using the CHA_2DS_2-VASc risk score increased the NRI index by 0.132 compared with the $CHADS_2$ risk score, while the NRI index decreased by 0.123 when the score was changed from $CHADS_2$ to R_2CHADS_2. The NRI index for mortality was positive for both the CHA_2DS_2-VASc and R_2CHADS_2 scores as compared with the $CHADS_2$ score, both in the general AF population (0.212 and 0.255, respectively) and in the subpopulation of members who did not purchase OACs (0.261 and 0.247, respectively).

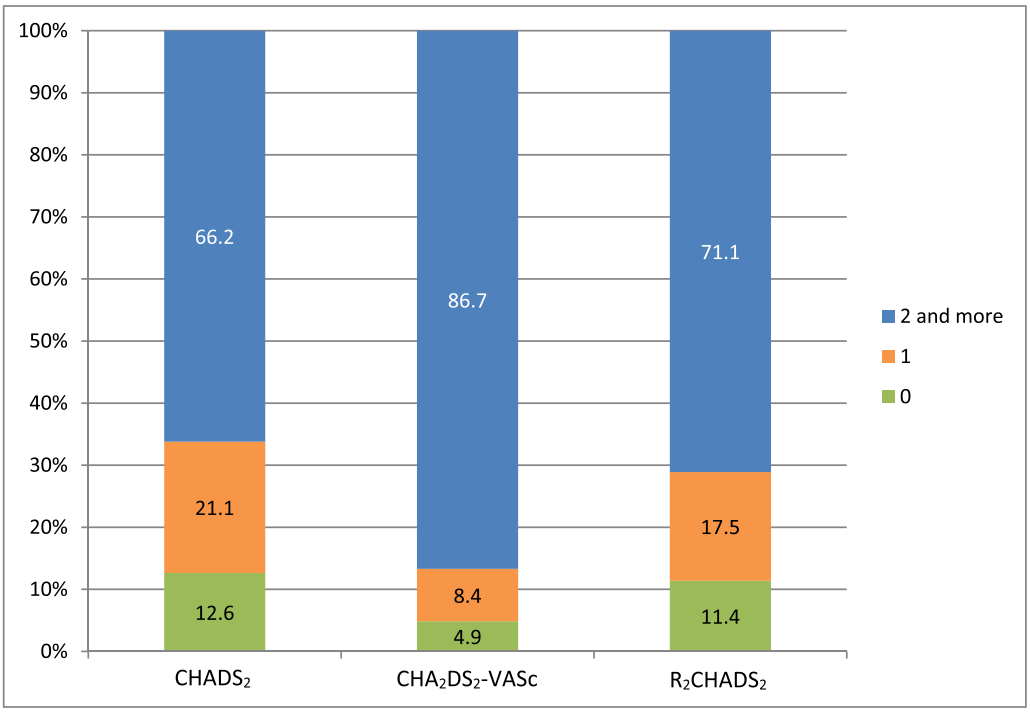

Figure 1. Distribution of risk strata (low, intermediate, and high) according to the different stratification scales.

Table 2
Incidence rates of ischemic stroke per 100 person-years based on the risk strata in the three stratification scales in the entire population and in the non oral anticoagulation users

	Clalit atrial fibrillation cohort n = 89,213			Non oral anticoagulation users n = 60,001		
	Population size	Number of cases	Incidence per 100 py	Population size	Number of cases	Incidence per100 py
Stroke						
N	89,213	5,752	2.00	60,001	3,537	1.89
$CHADS_2$						
0 Low risk	11,285	216	0.43	9,229	127	0.31
1 Intermediate risk	18,862	873	1.13	12,693	561	1.11
≥2 High risk	59,066	4,663	2.91	38,079	2,849	3.01
CHA_2DS_2-VASc						
0 Low risk	4,381	40	0.20	3,771	28	0.16
1 Intermediate risk	7,591	188	0.55	5,936	115	0.44
≥2 High risk	77,241	5,524	2.36	50,294	3,394	2.38
R_2CHADS_2						
0 Low risk	9,912	177	0.41	8,116	100	0.28
1 Intermediate risk	15,203	671	1.10	10,183	426	1.01
≥2 High risk	61,808	4,766	2.80	40,015	2,923	2.88
Mortality						
N	89,213	29,236	9.66	60,001	20,740	6.85
$CHADS_2$						
0 Low risk	11,285	851	1.67	9,229	635	1.44
1 Intermediate risk	18,862	3,681	4.66	12,693	2,695	4.14
≥2 High risk	59,066	24,704	14.30	38,079	17,410	9.52
CHA_2DS_2-VASc						
0 Low risk	4,381	208	1.03	3,771	177	1.03
1 Intermediate risk	7,591	626	1.82	5,936	462	1.74
≥2 High risk	77,241	28402	11.45	50,294	20101	13.33
R_2CHADS_2						
0 Low risk	9,912	675	1.53	8,116	506	1.15
1 Intermediate risk	15,203	2,483	3.81	10,183	1,794	2.75
≥2 High risk	61,808	25,435	13.90	40,015	17,978	9.83

Event within 30 to 2500 days post index date of atrial fibrillation diagnosis.

Table 3
Area under the curve of the 3 stratification scales and net reclassification index in comparison to $CHADS_2$ for stroke outcome in the entire population and in the non oral anticoagulation users

	Clalit atrial fibrillation cohort n = 89,213		Non oral anticoagulation users n = 60,001	
	Area under the curve (95% CI)	Net reclassification Index (95% CI)	Area under the curve (95% CI)	Net reclassification Index (95% CI)
Stroke				
$CHADS_2$	0.61 (0.59,0.61)	Ref	0.61 (0.60,0.62)	Ref
CHA_2DS_2-VASc	0.61 (0.60,0.61)	0.089 (0.060, 0.110)	0.61 (0.61,0.62)	0.132 (0.098, 0.166)
R_2CHADS_2	0.59 (0.58,0.60)	−0.083 (−0.110, −0.057)	0.60 (0.59,0.61)	−0.123 (−0.157, −0.090)
Mortality				
$CHADS_2$	0.64 (0.64, 0.65)	Ref	0.67 (0.66, 0.67)	Ref
CHA_2DS_2-VASc	0.58 (0.58, 0.58)	0.212 (0.204, 0.220)	0.60 (0.60, 0.60)	0.261 (0.251, 0.271)
R_2CHADS_2	0.64 (0.63, 0.64)	0.255 (0.245, 0.265)	0.66 (0.66, 0.66)	0.247 (0.234, 0.259)

Discussion

In this large cohort study of newly diagnosed AF, the proportion of patients classified as high, intermediate, or low risk varied considerably across the $CHADS_2$, CHA_2DS_2-VASc, and R_2CHADS_2 risk scores. Notably, all scores indicated a limited ability to classify patients into risk categories that corresponded to rates of both outcomes.

AF is considered to be the underlying cause of a significant proportion of all strokes[9] and stroke is subsequently the most feared complication of AF. Co-morbidities have a great impact on the risk of stroke[10] and are, therefore, incorporated into risk scores.[11] As the main purpose of stroke risk scores in patients with AF is to optimize a stroke prevention strategy, there is a need for the scores to identify patients at high risk to target for anticoagulant therapy, and to identify patients at low risk to prevent unnecessary treatment, with potential risk of bleeding. In practice, there are great differences across risk scores in assigning patients to the risk groups. In this study, the proportion of patients assessed at high risk for stroke increased absolutely by 20% when changing from the $CHADS_2$ score to the CHA_2DS_2-VASc score (66.2% to 86.7%), while moving from $CHADS_2$ to CHA_2DS_2-VASc decreased the proportions of patients designated as at low risk by over 2-fold (from 12.6% to 4.9%). Similar differences in the proportions of risk strata were also seen in other studies,[12–14] and are translated into substantial variations in OAC treatment recommendations.

The decision about which tool should be used to assess stroke risk may vary based on the threshold above which anticoagulant therapy should be prescribed. It has been previously demonstrated that the threshold is shifting[15]; while previously warfarin was the cornerstone of OAC treatment in patients with AF, a higher threshold was used, withholding OAC treatment from patients who might have otherwise received it, and then more recently to a lower threshold, after the introduction of the NOACs, which are considered to have a more favorable risk-benefit profile than warfarin.[16] Similar to this and others' findings,[3,17] we found that the CHA_2DS_2-VASc score is most likely better in identifying truly low-risk patients who should not be treated with OACs, suggesting that in an era of NOACs, the CHA_2DS_2-VASc score justifiably replaced the $CHADS_2$ score. Our results support this, as the NRI analyses findings indicated that CHA_2DS_2-VASc improved the net reclassification of patients as compared with the $CHADS_2$ score.

The predictive ability of all 3 scores had only a moderate capability of predicting stroke. Previous studies have also estimated the performance of different risk scores for stroke. Analyses from Denmark[18] and Sweden[19] found that the CHA_2DS_2-VASc score performed better than the $CHADS_2$ score, but the C-statistic estimates were similar (0.67 and 0.66, respectively).[19] Two other studies found that the $CHADS_2$ and CHA_2DS_2-VASc scores performed similarly in overall prediction of thromboembolism in patients with AF taking OAC therapy.[20,21] Similar to our study, these studies also demonstrate only a moderate discriminative ability in predicting stroke with C-statistics ranging between 0.56 and 0.67.[22,23] These results highlight the need for more accurate and reliable stroke stratification scores, mainly in light of the low rates of anticoagulation use seen in this study and other real world studies.[24]

In this study, based on the AUC analysis, we found that the R_2CHADS_2 score did not improve the predictive ability of $CHADS_2$. It was previously demonstrated that adding chronic kidney disease to the $CHADS_2$ and CHA_2DS_2-VASc risk scores did not independently improve the predictive value of the scores. [25]

As all-cause mortality remains a key concern in patients with AF, we tested the utilization of the stroke risk scores beyond its initial purpose: to predict mortality. It is presumed that patients with a high $CHADS_2$ score are at a high risk for mortality, as its components are all associated with increased mortality. Indeed, mortality rates increased dramatically with increasing scores, but although rates of mortality were higher than stroke, the 3 risk scores only modestly predicted the mortality outcome, with an AUC of 0.58 for the CHA_2DS_2-VASc and 0.64 for $CHADS_2$ and R_2CHADS_2, suggesting their potential use to predict mortality in patients with AF.

This study had several limitations that should be acknowledged. First, the study included CHS members with newly diagnosed AF between 2004 and 2015. During this study period, policies regarding treatment of AF and its associated co-morbidities (such as diagnosis of hypertension and diabetes, along with treatment guidelines) have changed. These changes may have temporal effects on the

risk of stroke, which were not taken into account. Additionally, the study period covered periods before and after the emergence of the NOACs, which might have also changed treatment patterns and could have altered stroke rates. Lastly, scores were assessed at the time of the initial AF diagnosis; however, in practice, clinicians often update the risk scores from visit to visit and may change their prevention stroke strategy accordingly and thus the updated scores may have better prediction ability. It is also important to emphasize the observational nature of this study, where unknown confounders are impossible to adjust for. Despite these limitations, the AUCs reported in our study are consistent with results obtained from other populations, and it is therefore unlikely that the limitations considerably affected the findings regarding the discriminating ability of the risk scores.

The available tools to assess stroke risk in patients with newly diagnosed AF are currently limited. A possible explanation could be that current risk scores do not account for the severity, duration, or treatment status of the AF condition or the severity of co-morbidities that are structured in the scores at the time of assessment. In addition, the scores may be missing additional factors, whether demographic or clinical, which may add predictive ability. This raises the need to build more powerful tools to better guide clinicians in choosing treatments for stroke prevention.

Authors' Contributions

Meytal Avgil Tsadok − concept and design, data interpretation, drafting article, critical revision of article, approval of article; Adi Berliner Senderey - data analysis, statistics, critical revision of article, approval of article; Orna Reges − acquisition of data, critical revision of article, approval of article; Morton Leibowitz - interpretation of data, critical revision of article, approval of article; Maya Leventer-Roberts - acquisition of data, critical revision of article, approval of article; Moshe Hoshen - data analysis, statistics, critical revision of article, approval of article; Moti Haim - concept and design, data interpretation, critical revision of article, funding secured, approval of article.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary materials

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