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Stroke risk scores for prediction of mortality and hemorrhages in atrial fibrillation patients

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Background: Atrial fibrillation (AF) is an emerging epidemic worldwide, responsible for a twofold increase in mortality, independent of other risk factors. Stroke prevention is the cornerstone of AF management. However, oral anticoagulation imposes an increased risk of bleeding. Several risk scores have been developed for estimating both the thromboembolic and the bleeding risks. The aim of the study was to determine the usefulness of different stroke risk scores as predictors of mortality and hemorrhagic events in AF patients.

Methods: We retrospectively enrolled 211 AF patients hospitalized in the Cardiology Ward of our tertiary hospital. The primary endpoints were mortality and non-minor bleeding events. The mean follow-up period was 378 days for bleeding events and 5 years and 1 month for mortality. For each patient, we evaluated the following stroke risk scores: $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, ABC, ATRIA, GARFIELD.

Results: The mean age in our cohort is 66, with a slight predominance of women (52.2%). For a CHA_2DS_2-VASc ≥ 4 as well as for a score of 2-3, 5-year survival was worse than for patients with a score of 0–1(chi-squared=8.13; p=0.01). Similarly, all subgroups of patients with an ABC <2%, had a worse 5-year survival when compared with an ABC score of ≥2% (chi-squared=12.85; p=0.005). C-statistics show a modest predictive value for mortality, for all stroke scores except Garfield, with similar AUCs, the highest being for CHA_2DS_2-VASc (AUC 0.656; p=0.0001). CHA_2DS_2-VASc also correlates with bleeding events, having a good predictive ability (AUC 0.723; 95%CI 0.658–0.782, p=0.001), mildly superior to HAS-BLED (AUC 0.674; 95% CI 0.523–0.825; p = 0.04) and very close to Garfield-bleeding (0.765; 95%CI 0.702–0.80; p=0.0001).

Conclusions: CHA_2DS_2-VASc is comparable to HAS-BLED and Garfield-bleeding in predicting bleeding events in AF patients. CHA_2DS_2-VASc and ABC correlate directly and consistently with mortality rate. For CHA_2DS_2-VASc, the AUCs for our endpoints are similar to the ones for stroke prediction, highlighting the potential of extending its applicability to various outcomes.

Key words: atrial fibrillation, bleeding, hemorrhage, mortality, stroke scores.

INTRODUCTION

Atrial fibrillation (AF) is an emerging epidemic worldwide, with an estimated lifetime risk of 1 in 3 adults [1].

Stroke prevention is the cornerstone of AF management. Because thrombotic risk is heterogenous, an individualized approach is required. An integrated, individualized approach is advocated in the most recent guidelines for the management of AF patients [2,3].

Because stroke risk factors do not confer equal risk, they have been used to formulate various stroke stratification schemes; the most validated and widely used scores are CHA_2DS_2-VASc and its predecessor, $CHADS_2$. Over the last years, various other stratification schemes have been proposed: ATRIA [4], ABC[5], Garfield[6], R_2CHADS_2[7].

Oral anticoagulant treatment (OAC) can prevent most ischemic strokes in AF patients and prolong survival. However, the residual mortality rate is still high (3–4% per year) [8].

OAC imposes an increased risk of bleeding. Many of the stroke risk factors, also increase bleeding risk (arterial hypertension, older age, female gender, etc.).

In contrast to stroke risk assessment schemes, scores for estimation of bleeding risk in AF patients are less well established. HAS-BLED is frequently used in clinical practice for estimating bleeding risk in anticoagulated patients. Still, various other bleeding risk scores could be considered. Garfield-bleeding and Garfield-mortality [6] are part of a recently-developed algorithm that simultaneously stratifies three different risks: mortality, thromboembolism, and bleeding. Recent data

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suggest its potential superiority to HAS-BLED [9] in predicting bleeding events.

We aimed to determine the usefulness of stroke risk scores as predictors of mortality and hemorrhagic events in AF patients. Our main objective was to evaluate the differential predictive value for a wide variety of stroke risk scores.

MATERIAL AND METHODS

We retrospectively evaluated for enrolment all AF patients hospitalized throughout the year 2015 in the Cardiology Ward in our Tertiary Hospital in Bucharest, Romania. Our final cohort included 211 patients. Fig. 1 shows the process of enrolment.

We included adult patients for which we had a follow-up after a minim of 6 months and maximum of 3 years (mean follow-up was 378 days). Mortality was evaluated in July 2020 (mean follow-up of 5 years, 1 month).

All data were collected from patients' files and hospital registries and so, many eligible patients were excluded for missing data.

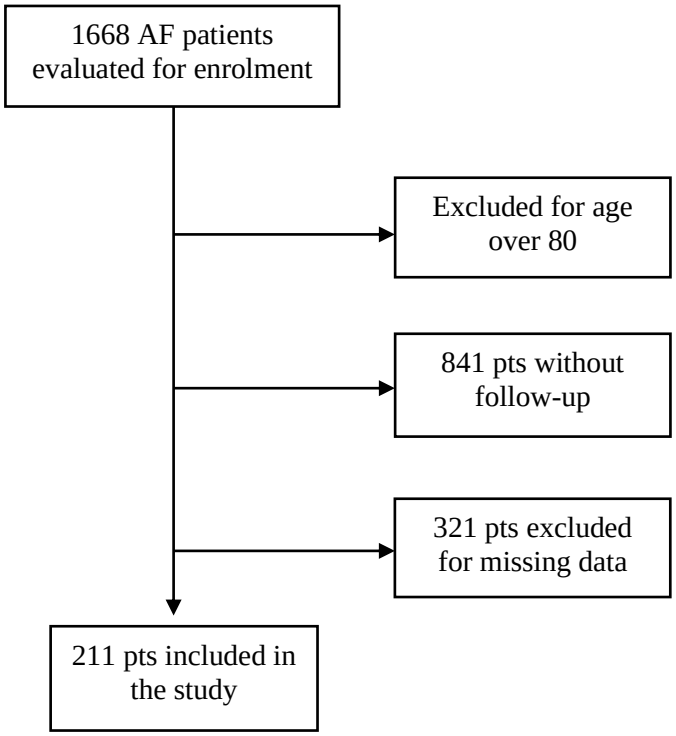


Fig. 1. Flow chart presenting the stages of pts selection.

ENDPOINT DEFINITION

Bleeding events included all types of non-minor hemorrhagic events. For standardization in defining bleeding events, we used the BARC classification [13] and included any bleeding that falls into types 2–5 of this classification.

We evaluated all-cause mortality with data obtained from the authorized national organization for person's record and database management.

STATISTICAL ANALYSIS

Clinical and demographic data are shown as means ± SD for continuous variables and percentages (frequencies) for categorical variables. Association of variables with adverse events was assessed using univariate and multivariate logistic regression. The predictive accuracy for each risk score was evaluated using C-statistics and the AUCs were compared using DeLong's method. Statistical analysis was performed using SPSS Statistics v23 and MedCalc v19.2 software.

RESULTS

The final cohort comprises a total of 211 AF patients. The mean age in our cohort is 66 years old, with a slight predominance of women (52.2%). Hemorrhagic events occurred in 12 (5.7%) patients and 69 (32.7%) pts died by the end of the follow-up period. Baseline characteristics of the study population are shown in Tables 1 and 2.

Table 1
Baseline characteristics. HTN=arterial hypertension. CHF=chronic heart failure. DM=diabetes mellitus

Baseline characteristics of the study population		N=211
Mean age (years)		66 (±8.79)
Gender (Male)		101 (47.8%)
AF type	Paroxysmal	43 (20.3%)
	Persistent	26 (12.3%)
	Permanent	142 (67.3%)
HTN		164 (77%)
CHF		62 (29.3%)
DM		53 (25.1%)
Dyslipidemia		72 (34.1%)
Prior stroke/TIA		21 (9.9%)

Table 2
Patients' chronic medication at enrolment

Medication at enrolment		N=211
Beta-blocker		160 (75.8%)
Ca channel blocker	DHP	23 (10.9%)
	Non-DHP	12 (5.68%)
AEI		158 (74.8%)
Digoxin		67 (31.7%)
Antiarrhythmic		44 (20.8%)
Loop diuretic		178 (84.3%)
Oral anticoagulation	VKA	142 (67.2%)
	NOAC	33 (15.6%)
Without OAC		36 (17%)
Statin		131 (62%)

Most patients are classified as having permanent AF, irrespective of age group (Fig. 2).

Patients' distribution based on stroke risk scores shows a predominance of small-medium scores (Figs. 3–8). The leftward deviation of the distribution curve is probably explained by the strict exclusion criteria.

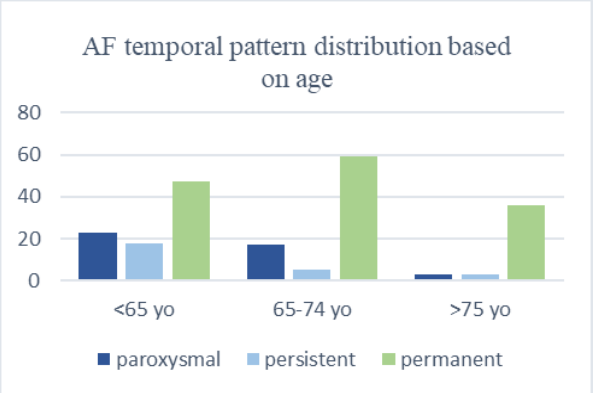


Fig. 2. AF type based on age group.

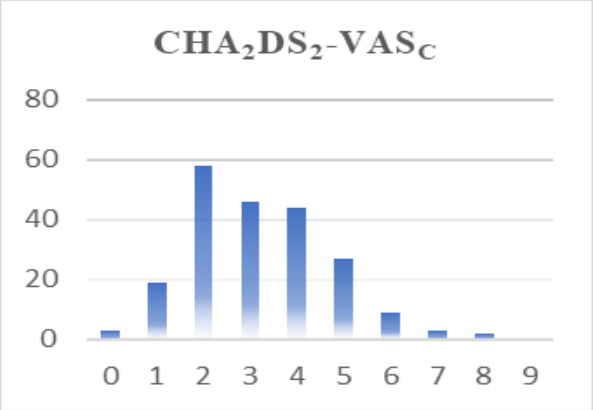


Fig. 3. Patients distribution based on CHA_2DS_2-VASc risk score.

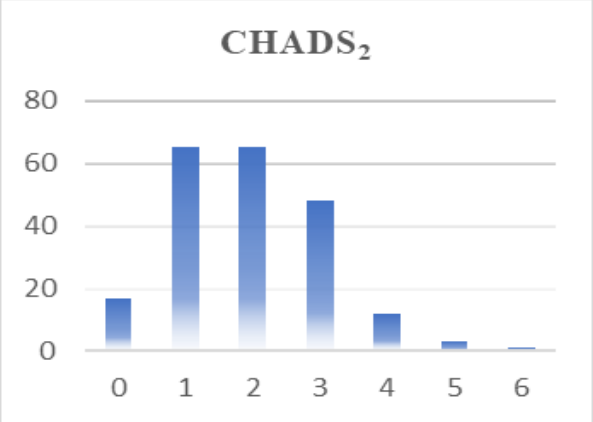


Fig. 4. Patients distribution based on $CHADS_2$ risk score.

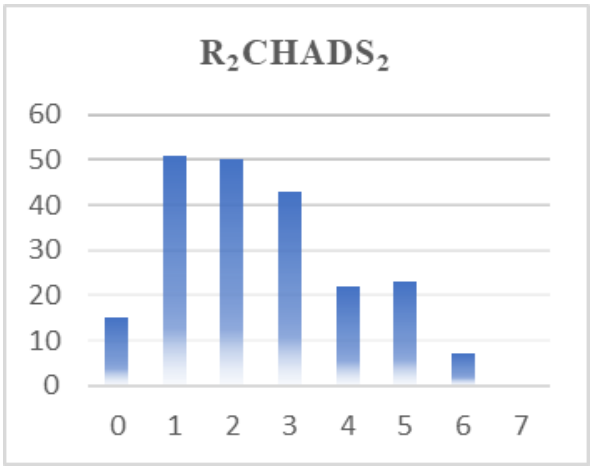


Fig. 5. Patients distribution based on R_2CHADS_2 risk score.

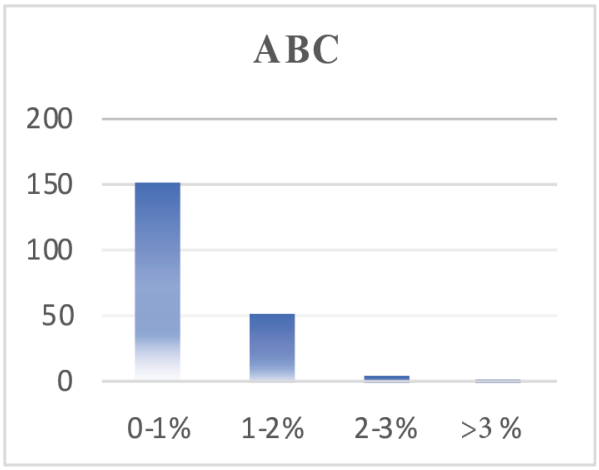


Fig. 7. Patients distribution based on ABC risk score.

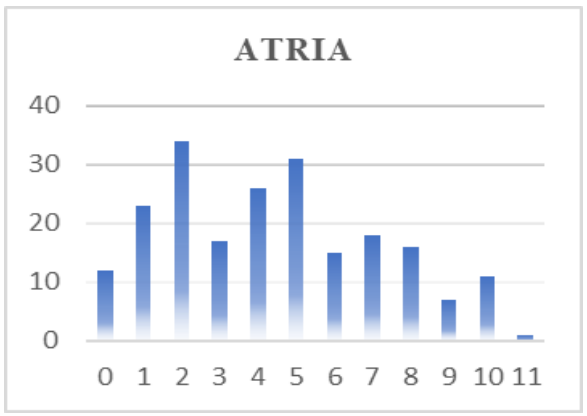


Fig. 6. Patients distribution based on ATRIA risk score.

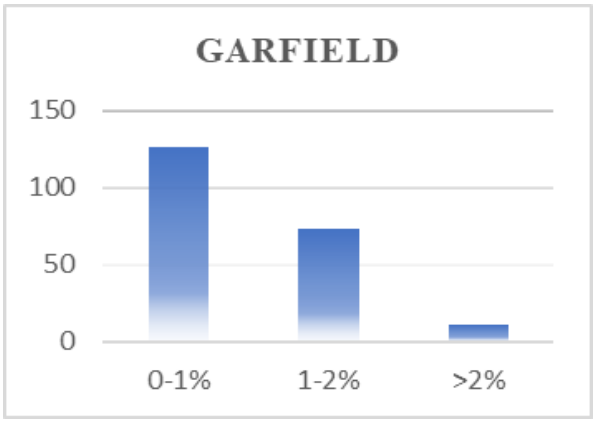


Fig. 8. Patients distribution based on Garfield-stroke risk score.

Bleeding events

At the end of the follow-up period, bleeding events occurred in 12 (5.7%) patients.

Of the stroke risk scores, only CHA_2DS_2-VASc reached the threshold of statistical significance as predictor of bleeding events in our cohort, the AUC showing a good correlation (0.723; 95%CI 0.658–0.782; p=0.001) (Fig. 9). Interestingly, C-statistics for CHA_2DS_2-VASc is superior to HAS-BLED (0.674; 95% CI 0.523–0.825; p=0.04) (Fig.10), and very similar to Garfield-bleeding (0.765; 95%CI 0.702–0.80; p=0.0001) (Fig.11).

For the rest of the stroke risk scores, our study failed to show a correlation with the risk of hemorrhagic events (Table 3).

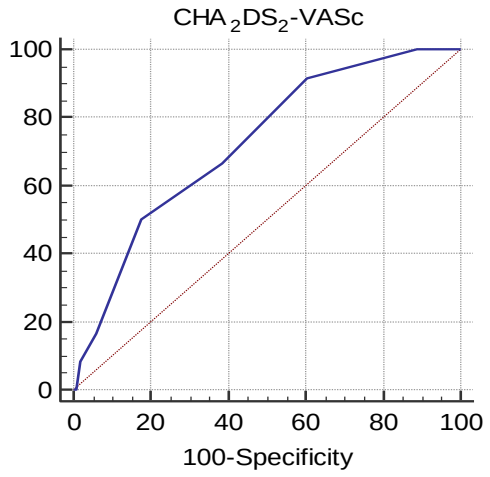


Fig. 9. ROC curve for CHA2DS2-VASc and bleeding events.

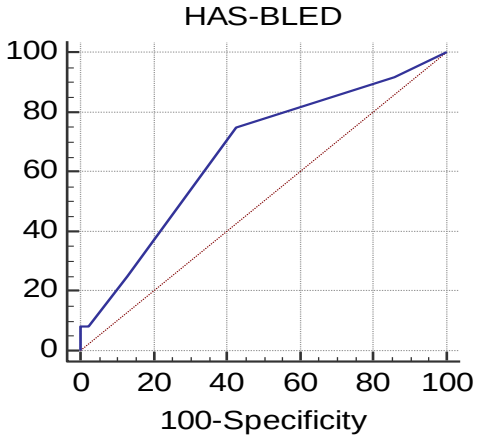


Fig. 10. ROC curve for HAS-BLED and bleeding events.

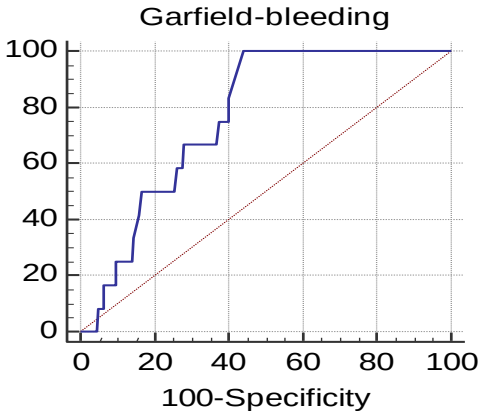


Fig. 11. ROC curve for Garfield-bleeding and hemorrhagic events.

Mortality

C-statistics for all stroke risk scores show a modest predictive value for mortality, except Garfield-stroke for which there was no correlation (Fig. 12). ATRIA (AUC 0.657; 95%CI 0.589–0.721; p=0.0001) and CHA_2DS_2-VASc (0.656; 95%CI 0.588–0.720; p=0.0001) have the highest predictive value, with very similar values for AUCs (Table 4), but still inferior to that of Garfield-mortality (AUC 0.747; 95% CI 0.683–0.804; p <0.0001). DeLong comparison of the ROC curves showed a statistically significant difference between Garfield-mortality and all stroke scores ($p<0.05$ for all), but between the pairs of stroke scores, the only significant difference was between CHA_2DS_2-VASc and Garfield-stroke (p=0.04).

CHA_2DS_2-VASc and ABC scoring systems were directly and consistently correlated with mortality rate (Figs. 13–14). For a CHA_2DS_2–VASc ≥ 4 as well as for a score of 2–3, 5-year survival was worse than for patients with a score of 0–1. Similarly, all subgroups of patients with an ABC <2%, had a worse 5-year survival when compared with an ABC score of ≥2% (Table 5).

Using univariate regression, we identified multiple independent predictors of mortality. In multivariate analysis, only age (p=0.005) and left ventricle end-diastolic diameter (LVEDD) (p=0.003) remained statistically significant (Table 6).

Table 3
Details of the ROC curve analysis for bleeding events

Risk score	AUC	95% CI	P
CHA_2DS_2-VASc	0.723	0.658 – 0.782	**0.0013**
$CHADS_2$	0.600	0.530 – 0.666	0.1367
R_2CHADS_2	0.599	0.529 – 0.665	0.1890
ABC	0.564	0.495 – 0.632	0.3838
ATRIA	0.652	0.584 – 0.716	0.0609
Garfield–stroke	0.528	0.458 – 0.597	0.779
HAS-BLED	0.674	0.523 – 0.825	**0.04**
Garfield–bleeding	**0.765**	0.702–0.82	**<0.0001**

Table 4
AUCs for mortality

Risk score	AUC	SE	95% CI	Se	Sp	Index J Youden	Z statistics	P
CHA_2DS_2-VASc	0.656	0.0383	0.588 – 0.720	76.8	45.7	0.2259	4.077	**0.0001**
$CHADS_2$	0.624	0.0392	0.555 – 0,690	76.81	47.18	0.2399	3.171	**0.0015**
R_2CHADS_2	0.627	0.0409	0.558 – 0,692	40.58	83.10	0.2378	3.102	**0.0019**
ABC	0.610	0.0433	0.540 – 0,676	39.13	83.1	0.2223	2.535	**0.0112**
ATRIA	0.657	0.0395	0.589 – 0,721	49.28	76.06	0.2533	3.985	**0.0001**
Garfield - stroke	0.543	0.0430	0.473 – 0.611	59.42	52.82	0.1224	0.996	0.3192

Table 5
Details of the logrank test for CHA_2DS_2-VASc and ABC

	CHA_2DS_2-VASc	**ABC**
Chi-squared	8.1316	12.8568
DF	2	3
Significance	P = 0.0171	P = 0.0050

Table 6
Independent predictors for mortality

	OR (95%CI)	**P**	**Chi-squared**
Age	1.0761 (1.0356 –1.1183)	< 0.0001	17.38
Anemia	6.3607 (2.1660 –18.6788)	0.0003	12.96
NYHA class	1.8559 (1.4418 t–2.3889)	<0.0001	26.7
sPAP	1.0195 (1.0019 – 1.0374)	0.02	4.9
Troponin	1.0572 (1.0039 – 1.1134)	0.026	4.98
LVEDD	1.0908 (1.0469 – 1.1364)	<0.0001	20.6
EF	0.95 (0.929–0.977)	0.0001	15.15

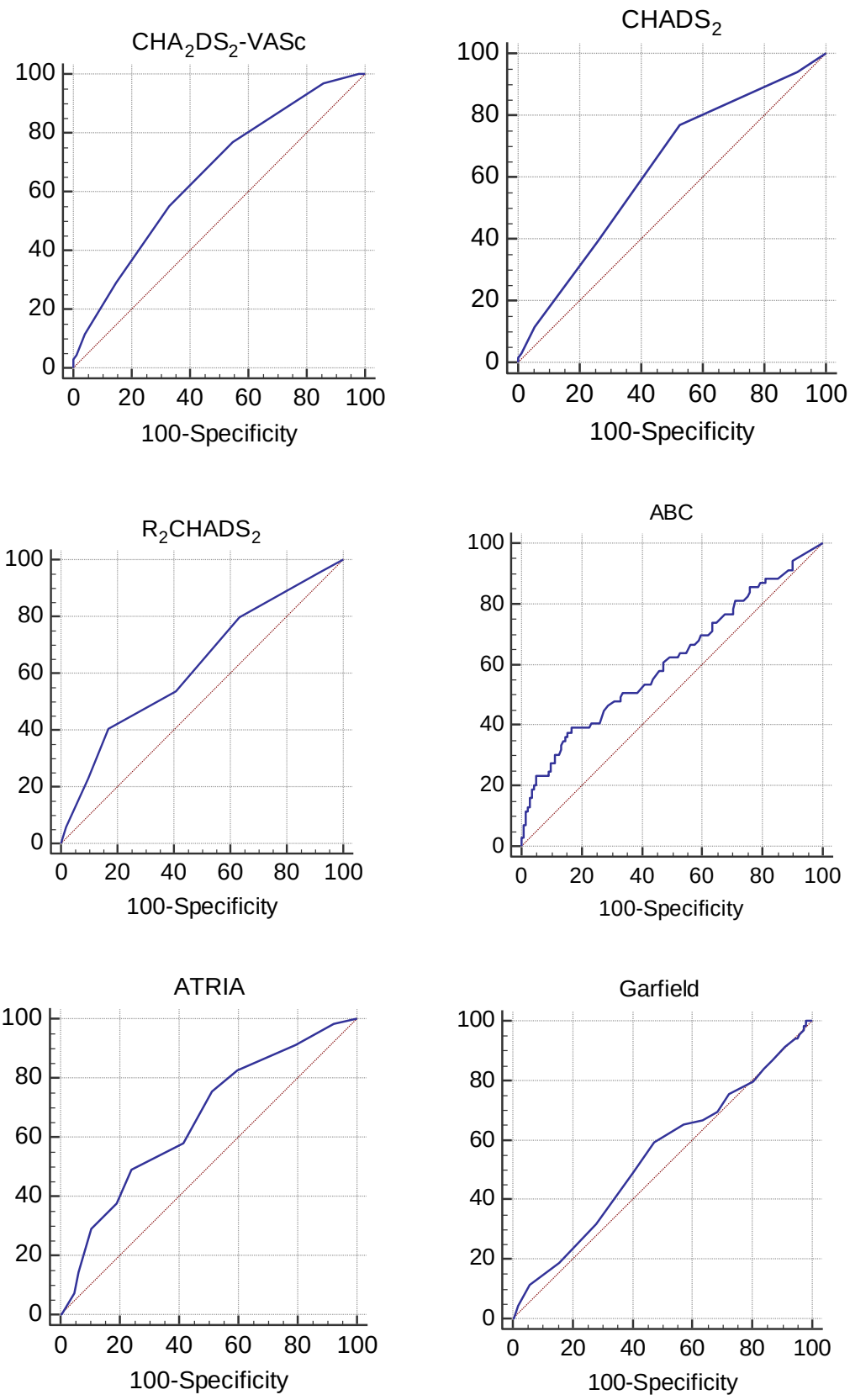


Fig. 12. ROC curves for mortality.

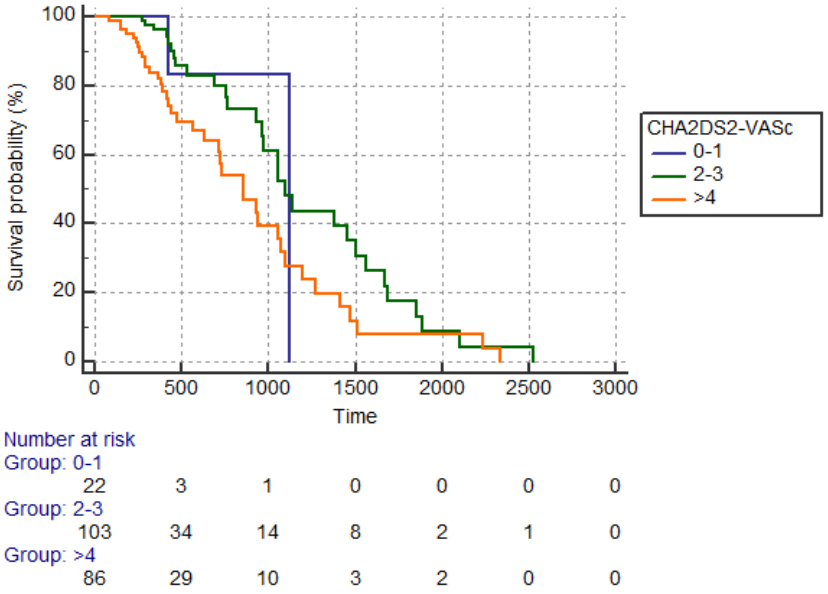


Fig. 13. Kaplan Meier curve of all-cause mortality by CHA2DS2-VASc score.

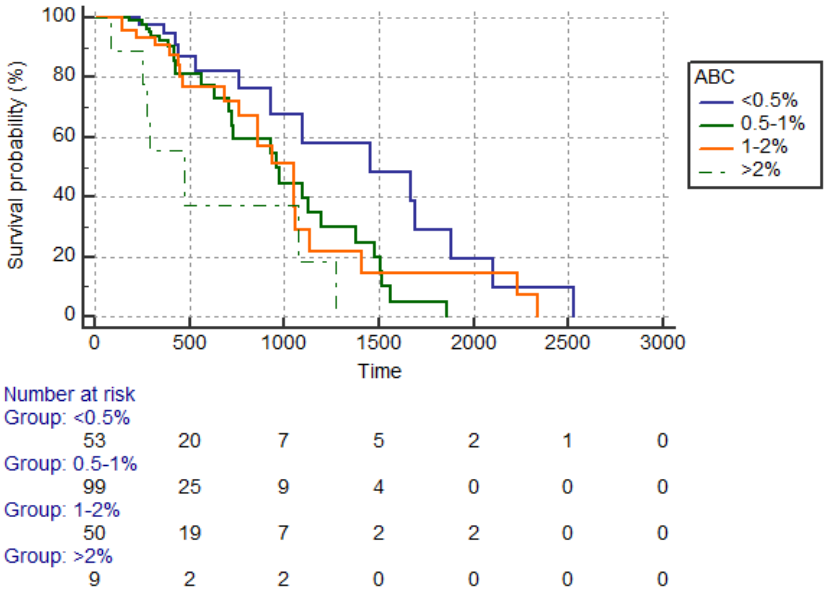


Fig. 14. Kaplan Meier curve of all-cause mortality by ABC score.

DISCUSSION

Stroke risk scores have been developed as schemes that combine the most important cardiovascular risk factors and various comorbidities. Extending the usefulness of a clinical tool, which is already used for all AF patients (as is CHA_2DS_2-VASc), is attractive because it avoids the use of other time-consuming tools; it also provides a better understanding of the risks, which could lead to improved therapeutic strategies.

In the presence of AF, it is particularly important to identify patients at high thromboembolic risk, through a simple and dynamic assessment. At the same time, anticoagulated AF patients are at

increased bleeding risk as well, and often OAC is discontinued due to fear of complications.

Thromboembolic risk scores are routinely used in clinical practice and current European guidelines recommend the use of CHA_2DS_2-VASc score to discriminate AF patients that need oral anticoagulant therapy. Still, its predictive power for stroke is not very high in validation studies, C-statistics for ischemic stroke prediction being 0.606 (0.513–0.699) for CHA_2DS_2-VASc [10]. In a large cohort [11] of non-anticoagulated patients from the Swedish Atrial Fibrillation study, the AUC was 0.67 (95%CI 0.66–0.68).

Prediction of bleeding events

Our study showed that CHA_2DS_2-VASc correlates with the risk of hemorrhagic events with a predictive power comparable to that of ischemic stroke.

However, literature data is conflicting; an analysis of the AMADEUS trial [12] showed an increase in the incidence of clinically significant bleeding with increasing CHA_2DS_2-VASc score, but without having statistical significance. These results were confirmed by another prospective, multicentric study [13] on a cohort of AF patients with PCI indication, for which CHA_2DS_2-VASc was not associated with hemorrhagic events.

Although several studies have shown a correlation between the $CHADS_2$ score and hemorrhagic risk, including important studies on large cohorts such as a subgroup analysis in the RE-LY study [14], for our cohort, the $CHADS_2$ score did not show statistical significance.

Given that a good correlation was obtained for CHA_2DS_2-VASc score in our cohort, we can speculate on the importance of the additional elements in this score, compared to $CHADS_2$. Of these, older age and female gender are known to increase the risk of bleeding. Triple or double antithrombotic therapy might be incriminated as well as a contributor to increased risk of bleeding in pts with a higher CHA_2DS_2-VASc based on atherosclerotic vascular disease.

Garfield-stroke score did not achieve notable results for this endpoint which can be explained by the existence of a specific Garfield score for bleeding risk. In our cohort, Garfield bleeding risk score had a good correlation with hemorrhages, comparable to HAS-BLED.

To date, we have not identified any studies evaluating ABC, ATRIA, or R_2CHADS_2 scores as predictors of hemorrhagic events in AF.

Prediction of mortality

The present study included predominantly patients with comorbidities, many of them elderly, influencing the frequency of adverse events including the mortality rate.

Several studies [14–18] have shown a direct and independent correlation between the value of CHA_2DS_2-VASc, $CHADS_2$, R_2CHADS_2 scores, and overall mortality in AF patients. Our study confirms these results, demonstrating a predictive value for mortality for all stroke risk scores except for Garfield. Of these, CHA_2DS_2-VASc, ABC, and ATRIA had the highest predictive power in our cohort.

For ABC score, so far we have identified only one study [19] that evaluates its predictive power for adverse events in AF pts. In our cohort, the ABC had the greatest influence on survival time, although the predictive power obtained using C-statistics were not superior to other stroke scores. A possible explanation for this result could be the relative benefit of biomarkers in discriminating survival time more than the absolute risk of death.

Limitations

The main limitation is related to the retrospective design of our study. Given the prevalence of AF, the small cohort size is also an important limitation as is the relatively short follow-up time for hemorrhagic events.

CONCLUSIONS

Except for Garfield, all stroke risk scores have a modest predictive value for 5-year mortality. Of these, ABC and CHA_2DS_2-VASc have the highest predictive power.

CHA_2DS_2-VASc correlates with bleeding events, with a predictive power comparable to established bleeding risk scores like HAS-BLED and Garfield-bleeding.

Due to the limitations of our study, these results need validation on larger cohorts and should be interpreted with caution.

Introducere: *Fibrilația atrială (FA) este o adevărată epidemie la nivel mondial, responsabilă de o creștere de două ori a mortalității, independent de alți factori de risc. Prevenția accidentului vascular cerebral este piatra de temelie a terapiei FA. Cu toate acestea, anticoagularea orală impune un risc crescut de sângerare. Au fost elaborate mai multe scoruri de risc pentru a estima atât riscul tromboembolic, cât și riscul de sângerare. Scopul studiului a fost de a determina utilitatea diferitelor scoruri de risc tromboembolic ca predictori ai mortalității și evenimentelor hemoragice la pacienții cu FA.*

Material și metode: *Am înrolat retrospectiv 211 pacienți cu FA internați în Secția de Cardiologie a spitalului nostru terțiar. Obiectivele principale au fost mortalitatea și evenimentele hemoragice non-minore. Perioada medie de urmărire a fost de 378 de zile pentru evenimentele hemoragice și de 5 ani și 1 lună pentru mortalitate. Pentru fiecare pacient, am evaluat următoarele scoruri de risc tromboembolic: $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, ABC, ATRIA, GARFIELD.*

Rezultate: *Vârsta medie în cohorta noastră este de 66 de ani, cu o ușoară predominanță a femeilor (52,2%). Pentru un CHA_2DS_2-VASc ≥ 4, precum și pentru un scor de 2–3, supraviețuirea la 5 ani a fost mai mică decât pentru pacienții cu un scor de 0–1 (Chi pătrat=8,13; p=0,01). În mod similar, toate subgrupurile de pacienți cu un ABC <2%, au avut o supraviețuire la 5 ani mai mică în comparație cu un scor ABC de ≥2% (Chi pătrat = 12,85; p = 0,005). C-statistics arată o valoare predictivă modestă pentru mortalitate, pentru toate scorurile cu excepția lui Garfield, cu arii de sub curba ROC similare, cea mai mare fiind pentru CHA_2DS_2-VASc (AUC 0,656; p=0,0001). CHA_2DS_2-VASc se corelează și cu evenimentele hemoragice, având o bună putere predictivă (AUC 0,723; 95%CI 0,658–0,782, p=0,001), ușor superioară față de HAS-BLED (AUC 0,674; 95% CI 0,523–0,825; p = 0,04) și foarte aproape de Garfield -H (hemorrhage) (0,765; 95%CI 0,702–0,80; p=0,0001).*

Concluzii: *CHA_2DS_2-VASc este comparabil cu HAS-BLED și Garfield-sângerări în prezicerea sângerărilor non-minore la pacienții cu FA. CHA_2DS_2-VASc și ABC se corelează direct și semnificativ cu mortalitatea. Pentru CHA_2DS_2-VASc, ariile de sub curbele ROC pentru obiectivele noastre sunt similare cu cele pentru predicția accidentului vascular cerebral, evidențiind potențialul de extindere a aplicabilității acestui scor de risc.*

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Conflict of interest disclosure: The authors declare that there are no conflicts of interest.

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