CHA2DS2-VASC Score Predicts the Risk of Stroke in Patients Hospitalized to the Internal Medicine Department Without Known Atrial Fibrillation

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BACKGROUND: The CHA2DS2-VASC score is used to assess the risk of cerebrovascular accident (CVA) in patients with atrial fibrillation (AF) or atrial flutter (AFL).

OBJECTIVES: We aimed to determine whether this score can determine the risk of CVA during the first year after hospitalization, in patients without known AF/AFL.

DESIGN: Single-center retrospective cohort.

PATIENTS: We included all patients aged $\geq$ 50 who were hospitalized between January 1, 2008, and December 31, 2018, to the internal medicine departments at the Chaim Sheba Medical Center, Israel. Exclusion criteria included history or new diagnosis of CVA, TIA, and AF/AFL and use of anticoagulation at any time.

MAIN MEASURES: Patients were stratified into 3 groups according to their CHA2DS2-VASC score (0–1, 2, or $\geq$ 3). The primary outcome was hospitalization with CVA/TIA within one year of the index hospitalization.

KEY RESULTS: Of the patients, 52,206 were included in the study. CVA/TIA occurred in 0.7%, 1.3%, and 1.7% of patients with a CHA2DS2-VASC score of 0–1, 2, and $\geq$ 3, respectively. Compared to a CHA2DS2-VASC score of 0–1, the HR for CVA/TIA occurrence for CHA2DS2-VASC scores of 2 and $\geq$ 3 was 1.77 (CI 1.42, 2.22) and 2.33 (CI 1.9, 2.85), respectively ($p < 0.001$ for both comparisons). Each additional CHA2DS2-VASC point increased the probability for readmission with CVA/TIA within 1-year by 26% (HR 1.26, CI 1.19, 1.32, $p < 0.001$). Similar trends were seen in subgroup analyses by gender, age, and renal function.

CONCLUSIONS: The CHA2DS2-VASC score is a predictor for CVA/TIA during the first year after hospitalization in patients without AF. High CHA2DS2-VASC scores warrant work-up for occult AF/AFL and other risk factors for CVA/TIA.

KEY WORDS: CVA/TIA; CHA2DS2-VASC; readmission; prediction.

BACKGROUND

Cerebrovascular event (CVA) is the second leading cause of death worldwide with an annual mortality rate of approximately 5.5 million people, and high morbidity with up to 50% of survivors suffering from a chronic disability. CVA also incurs substantial healthcare costs due to a high readmission rate, with more than half of the patients requiring readmission within 1 year.[1–5] Despite the continued evolution of reperfusion strategies for patients with acute ischemic stroke, effective primary prevention remains the most important goal in lowering the burden of stroke.[3,4]

Patients hospitalized in the internal medicine wards are usually older and have a high burden of chronic diseases, including risk factors for stroke. In the first year after hospitalization, the risk for re-hospitalization is increased, including re-hospitalizations because of acute CVA.[6] These readmissions pose a significant burden to patients and to the healthcare system, as they create significant mortality and morbidity. The latter is not only important regarding well-being, but also has an important economic impact on the health system. Therefore, identifying patients discharged from the internal ward who are at increased risk for readmission with CVA/TIA is important.

The CHA2DS2-VASC score was developed to predict the risk of thromboembolic events in patients with atrial fibrillation (AF) or atrial flutter (AFL) and is a straightforward and commonly used tool for treatment decisions on primary and secondary prevention in patients with AF.[5] In addition to predicting the risk for stroke, the CHA2DS2-VASC score was shown to be associated with higher readmission rates, increased mortality, length of stay, and admission costs in patients with AF.[7] Some studies showed a correlation between CHA2DS2-VASC score and atherosclerosis or left atrial thrombus (LAT),[8,9] raising a potential correlation of the CHA2DS2-VASC score with the risk for CVA in patients who do not have AF.

OBJECTIVE

In this study, we aimed to determine whether the CHA2DS2-VASC score can serve to assess the risk of readmission with CVA/TIA within one year, in patients discharged from the internal medicine department, who do not harbor known AF or AFL and are not treated with chronic anticoagulation (AC).

Design

A retrospective cohort study of patients hospitalized over 10 years in a single center. The study received approval from the local Helsinki committee.

Patients

We included all patients older than 50 who were admitted (index hospitalization) to any of the seven internal medicine departments at our center (the Chaim Sheba Medical Center, Tel Hashomer, Ramat-Gan, Israel) between January 1, 2008, and December 31, 2018. We did not include patients younger than 50 because the mechanism of CVA in these younger patients might be different than atherosclerosis or cardioembolic (i.e., thrombophilia, patent foramen ovale, use of contraceptives etc.). Patients with missing data, patients with a history or a new diagnosis of CVA, TIA, AF, or AFL at any time point during the index hospitalization (based on their electronic medical record diagnoses-list), patients with mechanical or bioprosthetic valve, patients who died during their index hospitalization, and patients who were treated with AC at any time point before or during the index hospitalization or were discharged with a recommendation for treatment with AC from the index hospitalization were excluded from the study. All patients included in the study had an ECG recording at admission with sinus rhythm and had no documented history of AF in their medical records.

Patients' information was recorded via electronic medical records, including drug therapy, admission, background, and discharge diagnoses.

Main Measures

CHA2DS2-VASC score was calculated for all patients during their index hospitalization and the patients were divided into 3 groups according to a CHA2DS2-VASC score of 0–1 (low risk), 2 (medium risk), and $\geq$ 3 (high risk). The score was calculated based on: https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk[5]. We then identified retrospectively all patients who were re-admitted to our institution with ischemic CVA/TIA within 1 year of their index hospitalization. Patients with hemorrhagic CVA were excluded. The rate of readmission with CVA/TIA was calculated for each CHA2DS2-VASC group.

Patients' characteristics were presented as n (%) for categorical variables, and as mean (sd) or median [IQR] for normal/non-normal distributed continuous variables. A chi-square test for trends was used for comparison of categorical
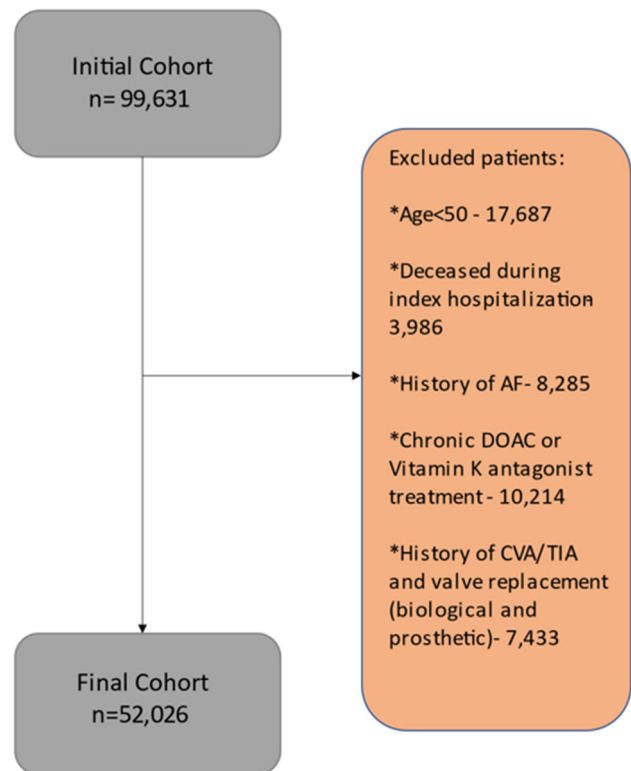
variables. Analysis of variance with 1 degree of freedom was performed for comparison of normally distributed continuous variables, and Kendall rank correlation, for non-normal distribution.

Survival curves were presented, and the Kaplan–Meier log-rank test was used to test the variable of interest on survival. Post-hoc comparisons were conducted using R::survminer package with the Benjamini–Hochberg adjustment for p-value.

Predefined subgroup analyses were performed according to gender, glomerular filtration rate (GFR) (GFR $\leq$ 60 ml/min/1.73m^2 or > 60 ml/min/1.73m^2), and age (< 75 years or $\geq$ 75 years).

All tests were conducted at a two-sided overall 5% significance level (aa = 0.05). All analyses were performed using R software (R Development Core Team, version 4.0.0, Vienna, Austria).

RESULTS

A total of 99,631 patients were hospitalized to the internal medicine wards between January 1, 2008, and December 31, 2018. After exclusion as detailed above, 52,206 patients were included in the final study population [Fig. 1]. Their baseline characteristics are shown in Table 1. Comparison of the baseline characteristics according to the outcome (CVA/TIA) is shown in Supplementary Table 1. The median age was 72 and 26,761 (51.4%) of the patients were men. A significant
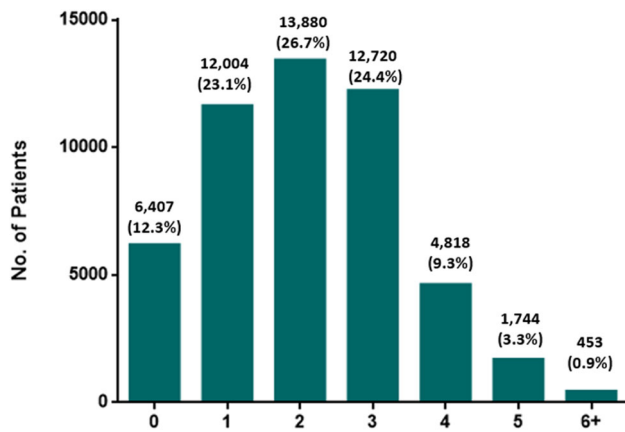

Fig. 1 Patient selection flow chart

Fig. 2 The distribution of the CHA2DS2-VASC score at the index hospitalization

proportion of the cohort had background hypertension (16.1%), ischemic heart disease (10.6%), and/or diabetes mellitus (9.7%).

The distribution of the CHA2DS2-VASC score at the index hospitalization is shown in Fig. 2. After grouping the patients as described, there were a total of 18,411 (35.3%), 13,880 (26.6%), 19,735 (37.8%) patients with a low (0–1), medium (2), or high (≥ 3) CHA2DS2-VASC scores, respectively. The 1-year all-cause mortality rate was 13.8%, 19.2%, and 20.7% according to the CHA2DS2-VASC group (low vs. medium vs. high, respectively, $p < 0.001$).

Cerebrovascular Event Rate

During the first year after the index hospitalization, there were a total of 640 (1.2%) CVA/TIA cases: $N = 133$ (0.7%), $N = 177$ (1.3%), and $N = 330$ (1.7%) in patients with a CHA2DS2-VASC score of 0–1, 2, and ≥ 3, respectively (p for trend = 0.064). The event rate of CVA/TIA per 100 patient-years was 0.8, 1.48, and 1.96 according to the CHAD2S2-VASC group (low risk vs. medium risk vs. high risk), respectively. The cumulative incidence of CVA/TIA according to the CHA2DS2-VASC group at 1 year follow-up is presented in the Kaplan–Meier survival analysis [Fig. 3].

Compared to a low CHA2DS2-VASC score (0–1), the HR for the occurrence of CVA/TIA for medium and high CHA2DS2-VASC score was 1.77 (CI 1.42, 2.22) and 2.33 (CI 1.9, 2.85), respectively ($p < 0.001$ for both comparisons). Each additional CHA2DS2-VASC point increased the probability for readmission with CVA/TIA within 1-year by 26% (HR 1.26, CI 1.19, 1.32, $p < 0.001$).

Subgroup Analysis

We also assessed the correlation between CHA2DS2-VASC score and CVA/TIA according to gender, renal function, and age. The number of patients in each group, the CHA2DS2-VASC scores, and rate of readmission with CVA/TIA within 1 year are detailed in Table 2.

Women and men had similar rates of CVA/TIA (1.2% in women versus 1.3% in men, $p = 0.56$), while patients older than

Table 1 Baseline Characteristics of the Study Population According to CHA2DS2-VASC Scores

|		All N = 52,026	Low (CHA2DS2-VASC = 0–1) N = 18,411	Medium (CHA2DS2-VASC = 2) N = 13,880	High (CHA2DS2-VASC ≥ 3) N = 19,735	*p*-value (trend)
Males (%)		26,761 (51.4)	12,926 (70.2)	8,537 (61.5)	5,298 (26.8)	< 0.001
Age (IQR—years)		72 (62–81)	61 (56, 65)	73 (67, 81)	81 (76, 86)	< 0.001
Age > 65 (%)		35,829 (68.9)	4,804 (26.1)	12,079 (87)	18,946 (96)	< 0.001
Age > 75 (%)		21,979 (42.2)	0	6,222 (44.8)	15,757 (79.8)	< 0.001
Background diagnosis (%)	HTN	8,373 (16.1)	445 (2.4)	1,401 (10.1)	6,527 (33.1)	< 0.001
	Dyslipidemia	5,529 (10.6)	863 (4.7)	1,101 (7.9)	3,565 (18.1)	< 0.001
	IHD	5,517 (10.6)	1,055 (5.7)	1,109 (8)	3,353 (17)	< 0.001
	Diabetes	5,049 (9.7)	324 (1.8)	811 (5.8)	3,914 (19.8)	< 0.001
	Anemia	2,508 (4.8)	448 (2.4)	515 (3.7)	1,516 (7.7)	< 0.001
	CKD	1,950 (3.7)	314 (1.7)	498 (2.9)	1,238 (6.3)	< 0.001
	Smoker	2,205 (4.2)	807 (4.4)	513 (3.7)	885 (4.5)	0.93
	COPD	1,278 (2.5)	324 (1.8)	321 (2.3)	633 (3.2)	< 0.001
	CHF	1,145 (2.2)	61 (0.3)	133 (1)	951 (4.8)	< 0.001
	PVD	716 (1.4)	30 (0.2)	92 (0.7)	594 (3)	< 0.001
GFR ≤ 60 (missing data—2,686)		22,701 (46)	5,098 (29.4)	6,212 (47.2)	11,391 (60.5)	< 0.001
Primary diagnosis of index hospitalization (10 most common)	Chest pain	5,454 (10.5)	2,597 (14.1)	1,357 (9.8)	1,500 (7.6)	< 0.001
	Pneumonia	4,782 (9.2)	1,400 (7.6)	1,372 (9.9)	2,010 (10.2)	0.001
	IHD	3,483 (6.7)	878 (4.8)	740 (5.3)	1,865 (9.5)	< 0.001
	Anemia	3,450 (6.6)	929 (5)	895 (6.4)	1,626 (8.2)	< 0.001
	UTI	3,175 (6.1)	702 (3.8)	884 (6.4)	1,589 (8.1)	< 0.001
	HTN	2,959 (5.7)	226 (1.2)	518 (3.7)	2,215 (11.2)	< 0.001
	Renal disease	2,903 (5.6)	732 (4)	766 (5.5)	1,405 (7.1)	< 0.001
	Syncope	2,449 (4.7)	802 (4.4)	723 (5.2)	924 (4.7)	0.16
	CHF	2,264 (4.4)	131 (0.7)	294 (2.1)	1,839 (9.3)	< 0.001
	Fever	2,017 (3.9)	953 (5.2)	552 (4)	512 (2.6)	< 0.001
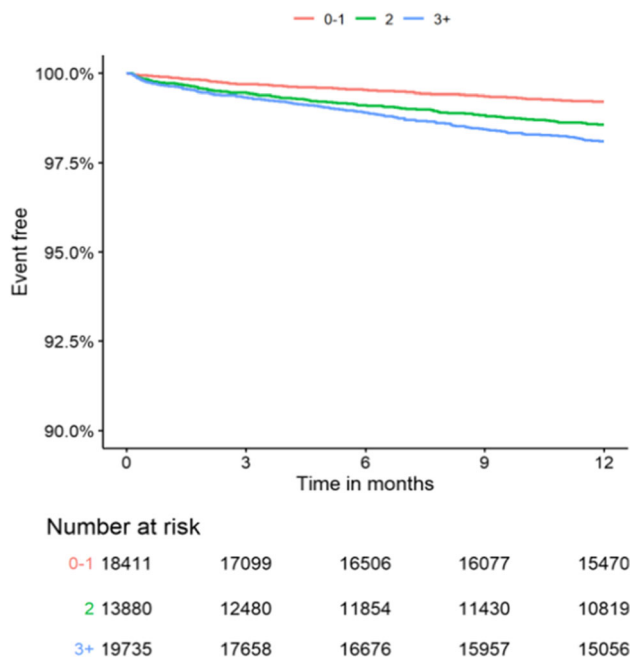
Fig. 3 Kaplan–Meier of TIA/CVA according to CHA2DS2-VASC groups (low vs medium vs high)

75 had a higher rate of CVA/TIA compared to younger patients (1.8% versus 0.8% respectively, $p < 0.001$) and patients with a low GFR had increased risk for CVA/TIA compared to higher GFR (1.6% vs 1%, respectively, $p < 0.001$) (Table 2). The survival analysis of CVA according to the CHA2DS2-VASC group is presented in Fig. 4; compared to the group with a low-risk score, medium- and high-risk scores correlated with the risk of CVA/TIA in all subgroups, except for patients older than 75. In patients younger than 75, only the high-risk score was significantly different than the low-risk score.

DISCUSSION

Our findings show that in patients older than 50 years old without AF, who are hospitalized in the internal medicine ward, the CHA2DS2-VASC score is associated with the risk of re-hospitalization with CVA/TIA within 1 year. This finding was consistent in patients younger than 75, regardless of gender and renal function.

Our study suggests that patients who are discharged from hospitalization in the internal medicine ward and who have a medium to high CHA2DS2-VASC score should be assessed rigorously for risk factors for CVA, i.e., occult AF, cerebral atherosclerosis, or left atrial thrombus, and treated intensively for risk factors for atherosclerosis, such as hypertension, hyperlipidemia, diabetes mellitus, and peripheral vascular disease.

Our results are in line with previous studies that showed that CHA2DS2-VASC and CHADS2 scores are associated with a higher risk of CVA/TIA in the absence of AF.[10–14] Most of these studies had a small sample size,[13] or were performed on specific populations such as patients with heart failure[10] or coronary artery disease,[11,12,14] thus limiting their generalizability to the general population. Saliba et al.[15] demonstrated in a big community database, that the incidence of CVA/TIA in patients without AF above the age of 50 is higher with increasing CHA2DS2-VASC scores. Our study expands this data to hospitalized patients.

Subgroup analysis in our cohort showed that the risk for CVA/TIA in patients with low GFR (≤ 60 ml/min/1.73m^2) was elevated compared to patients with higher GFR. This finding demonstrates the known importance of chronic kidney disease as a strong independent risk factor for CVA,[16] which is highlighted in the relatively new R(2)CHADS(2) score, which was found to be superior to the CHA2DS-VASC score in predicting CVA in patients with AF and renal dysfunction.[17]

In the gender subgroup analysis, we found a linear relationship between the CHA2DS-VASC score and the risk for CVA/TIA in women, with the survival curve of the medium CHA2DS-VASC group more akin to the survival curve of the low CHA2DS-VASC group than that of the high CHA2DS-VASC group. In men, medium and high CHA2DS-VASC groups acted similarly [Fig. 4]. This finding indicates that

Table 2 Number of Patients in Each Subgroup, Their Distribution by CHA2DS2-VASC Scores and Rates of Readmission with CVA/TIA Within 1 Year

| CHA2DS2-VASC		Men $n = 26,761$	Women $n = 25,265$	GFR ≤ 60 $n = 22,701$	GFR > 60 $n = 26,639$	Age < 75 $n = 30,047$	Age ≥ 75 $n = 21,979$
Low [0–1] (%)		12,926 (48.3)	5,485 (21.7)	5,098 (22.5)	12,250 (46)	18,411 (61.3)	0 (0)
Medium [2] (%)		8,537 (31.9)	5,343 (21.1)	6,212 (27.4)	6,958 (26.1)	7,658 (25.5)	6,222 (28.3)
High [$\geq$ 3] (%)		5,298 (19.8)	14,437 (57.1)	11,391 (50.2)	7,431 (27.9)	3,978 (13.2)	15,757 (71.7)
Readmission with	Total	337 (1.3)	303 (1.2)	359 (1.6)	264 (1)	255 (0.8)	385 (1.8)
CVA/TIA (%)	Low [0–1] (%)	109 (0.8)	24 (0.4)	49 (1)	79 (0.6)	133 (0.7)	N/A
	Medium [2] (%)	136 (1.6)	41 (0.8)	91 (1.5)	78 (1.1)	67 (0.9)	110 (1.8)
	High [$\geq$ 3] (%)	92 (1.7)	238 (1.6)	219 (1.9)	107 (1.4)	55 (1.4)	275 (1.7)
Comparison (*p*-value)	Low vs medium	< 0.001	0.023	0.01	< 0.001	0.19	N/A
	Low vs high	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	N/A
	Medium vs high	0.56	< 0.001	0.03	0.08	0.02	0.75
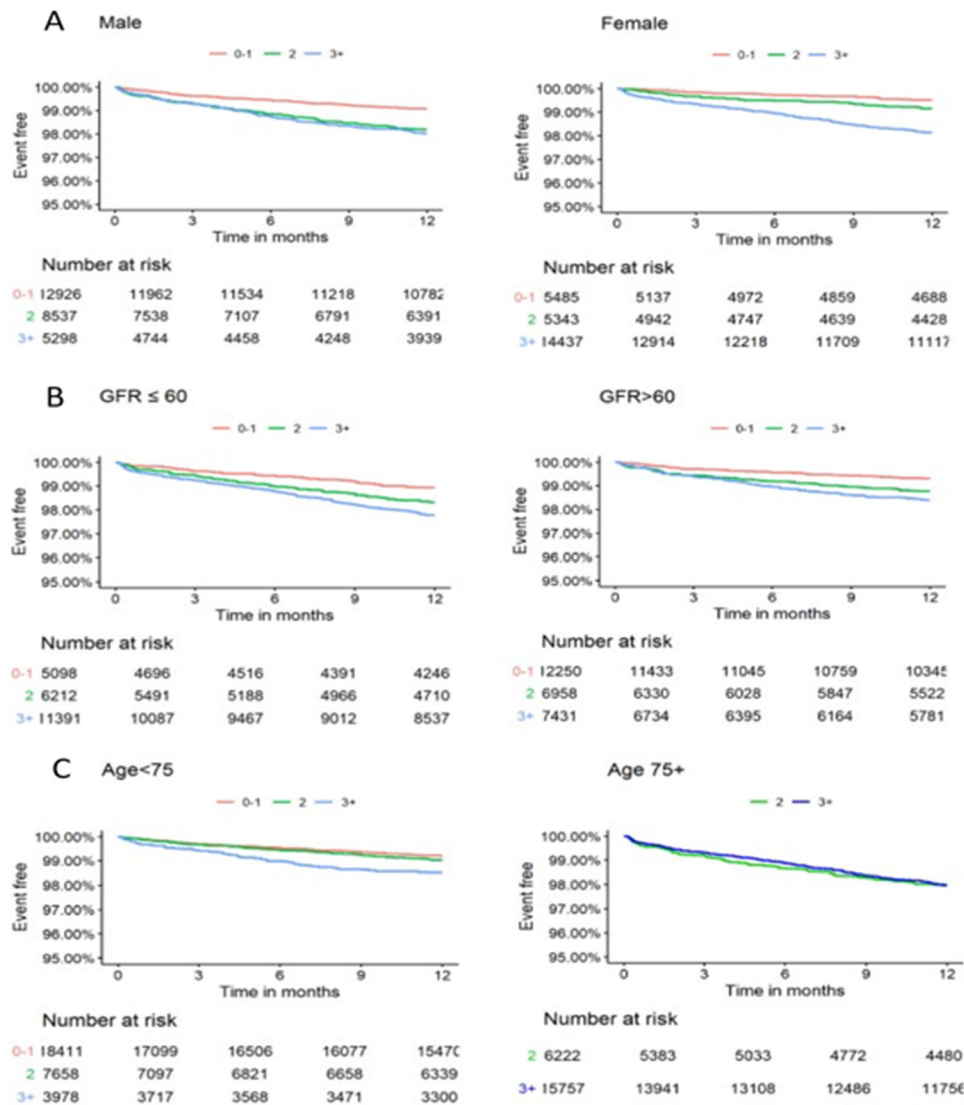
Fig. 4 Kaplan–Meier of TIA/CVA according to CHA2DS2-VASC groups (low vs medium vs high) in subgroup analysis. A Subgroup analysis by gender; B subgroup analysis by GFR; C subgroup analysis by age

the CHA2DS-VASC score may overestimate the risk for thromboembolic events that are attributed to female sex, as demonstrated previously,[18,19] while in men a CHA2DS-VASC score of 2 and higher may already signify a significant risk for CVA/TIA.

Since many cryptogenic ischemic strokes are likely to have an embolic mechanism and occult AF may underlie a significant proportion of these events, thought must be given to improve detection of AF. Recently, Diederichsen et al.[20] reported the low sensitivity of routine AF detection strategies compared to an implantable loop recorder for a period of 3 years, with a single 10-s ECG yielding a sensitivity of 1.5% for AF detection, increasing to only 34% for a single 30-day continuous monitoring device. Gladstone et al. showed that screening for AF in patients above the age of 75 with wearable ECG monitors increase AF detection by tenfold compared to standard practice, and lead in many instances to initiation of AC therapy.[21] These findings, together with the

results of our study, may justify a thorough investigation for occult AF in patients with high CHA2DS2-VASC scores, especially in the older population, by using advanced techniques such as longer monitoring of heart rhythm.

Current guidelines recommend initiation of AC treatment for primary prevention in AF patients with a CHA2DS2-VASC score of 2 or above, as this score puts them at a 2.2% risk for ischemic stroke per 100 patient-years and a 2.9% risk for stroke/TIA/peripheral emboli per 100 patient-years.[22] In our study, the rate of CVA/TIA within 1 year in the high score group was 1.96%.

Limitations

Our study is a single-center study, thus limiting its generalizability. Additionally, data on patients that were re-admitted after the index hospitalization with CVA/TIA to a different institution was not available to us, as we did not have access to this data. This caveat may cause underestimation of the rate of

stroke in the first year after hospitalization. Since our medical center is the largest in Israel, we can assume that the total number of these patients was relatively low and did not significantly impact our results. It is important to note that our data refer only to patients who were hospitalized and cannot be generalized to ambulatory patients. Additionally, we did not have data on the incident of new-onset AF during the first year after the index hospitalization and on the mechanism of ischemic stroke (cardioembolic vs. thrombotic or atherosclerotic).

CONCLUSION

Our study implies that the CHA2DS2-VASC score can be used to assess the risk for re-hospitalization within 1 year with CVA/TIA in patients hospitalized without AF. These results should raise the awareness of physicians and hospitalists that hospitalization for any reason should be used as an opportunity to assess the CHA2DS2-VASC score, in order to identify the risk of stroke and to assess for occult stroke culprits in patients with a medium to high CH2DS2-VASC score.

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Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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