Is CHA_2DS_2-VASc Score Different in Patients with Non-valvular Atrial Fibrillation Suffering from Cerebral and Non-cerebral Thromboembolism?CHA_2DS_2-VASc Score in Thromboembolism

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Abstract

Background: Thromboembolic complication is directly related to CHA_2DS_2-VASc score in patients with non-valvular atrial fibrillation (NVAF). In this study we compared the CHA_2DS_2-VASc score and in-hospital mortality between NVAF patients with non-cerebral thromboembolism and those with stroke.

Methods: We retrospectively reviewed medical records of 213 patients with NVAF who experienced stroke and 115 patients with NVAF who experienced non-cerebral thromboembolism between 2010 and 2015. In all patients, CHA_2DS_2-VASc score before the event was calculated.

Results: The mean CHA_2DS_2-VASc score was similar in patients with stroke (4.52±1.66) and those with non-cerebral thromboembolism (4.29±2.02) (p=0.196). In-hospital mortality rate was similar between the groups (19% vs. 17%, p=0.756). The rates of coronary artery disease (52% vs. 38%, p=0.014), prior transient ischemic attack (16% vs. 5%, p=0.001), and prior non-cerebral thromboembolism (18% vs. 3%, p<0.001) were higher in patients with non-cerebral thromboembolism. Warfarin (55% vs. 14% p<0.001) and antiplatelet use (56% vs. 40%, p=0.004) was more common in the non-cerebral embolism group, while non-vitamin K antagonist oral anticoagulant (NOAC) use was more common in the stroke group (15% vs. 7% p=0.026).

Conclusions: The patients with stroke had similar CHA_2DS_2-VASc score and in-hospital mortality compared to patients with non-cerebral thromboembolism.

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia encountered in clinical practice [1]. Atrial fibrillation can result in complications such as heart failure and decrease in the quality of life that are associated with morbidity and mortality. Apart from these complications arterial thromboembolism is another important complication of AF [2]. Prevention and treatment of thromboembolic complications is one of the main goals of AF management [3]. Stroke is the most feared and well-known thromboembolic event associated with AF [4],[5]. However, non-cerebral peripheral embolism is another important cause of morbidity and mortality in AF [2]. Besides, AF is the most important risk factor for non-cerebral embolism and an important prognostic marker [6]-[9].

The CHA_2DS_2-VASc score [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (double), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] is the most commonly used method to evaluate the risk stratification of thromboembolism in AF. Although the use of CHA_2DS_2-VASc score has been recommended to estimate thromboembolic events in patients with AF, observational and randomized clinical studies have mostly focused on the prevention of stroke [10]. Also in clinical practice, CHA_2DS_2-VASc score is used with particular focus on the prevention of stroke in patients with non-valvular AF (NVAF). The risk level for thromboembolic events based on the CHA_2DS_2-VASc score is not sufficiently known in

Key Words

CHA_2DS_2-VASc score, stroke, non-cerebral embolism, non-valvular atrial fibrillation.

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patients with non-cerebral arterial thromboembolism. As a result, it is not known whether patients with cerebral or non-cerebral thromboembolism have different levels of thromboembolic risk as assessed by the CHA_2DS_2-VASc score.

In this study we compared the thromboembolic risk level based on CHA_2DS_2-VASc score and in hospital mortality between NVAF patients with stroke and those with non-cerebral thromboembolism.

Methods

The present study retrospectively reviewed medical records of the patients, who experienced stroke or non-cerebral embolism due to NVAF between 2010 and 2015. The diagnosis of stroke was established by demonstration of the infarcted brain area using cranial computed tomography or cranial diffusion magnetic resonance imaging in patients developing sudden onset of weakness and loss of sensation, speaking and understanding disorder, impaired consciousness, and confusion. If clinical symptoms of stroke have resolved within the first 24 hours, patients with or without a demonstrable infarct area were regarded as transient ischemic attack [11].

The diagnosis of non-cerebral peripheral arterial embolism was confirmed by the presence of the symptoms and findings of acute ischemia with an onset five days before hospital admission, observation of a short occlusion in arterial bifurcation and trifurcation line consistent with a thrombus formation using Doppler ultrasonography and angiographic methods (intraarterial digital subtraction angiography, computed tomography (CT), magnetic resonance (MR) angiography), and detection of an embolus with defined margins during surgery. Acute embolism affecting visceral organs was diagnosed by the presence of acute onset of symptoms and demonstration of embolic occlusion using imaging methods such as CT and MRI.

Patients with valvular AF, intraventricular thrombus, infective endocarditis, pulmonary embolism and deep vein thrombosis, patients with a prosthetic valve, patients with a history of critical leg ischemia, graft occlusion, and patients with a vascular aneurysm were excluded. Accordingly, 213 patients with stroke and 115 patients with non-cerebral embolism were included in the study. The two groups were compared with respect to age, demographic risk factors, previous use of antiplatelet and anticoagulant drugs, CHA_2DS_2-VASc score [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] and mortality. CHA_2DS_2-VASc score, antiplatelet and anticoagulant use, hospitalization procedure and mortality rate were compared between the patients according to the localization of non-cerebral embolism.

Statistical analysis

Statistical analysis was performed using the SPSS (version 15.0, SPSS Inc., Chicago, Illinois) software package. Continuous variables were expressed as mean ± standard deviation (mean ± SD), and categorical variables were expressed as percentage (%). The Kolmogorov-Smirnov test was performed to test whether variables were normally distributed. Inter-group differences were evaluated using Student's t-test for normally distributed continuous variables and using Mann-Whitney U-test for variables that did not show normal distribution. ANOVA was used to compare continuous variables between more than two groups. Chi-square test was used for the comparison of categorical variables. A two-tailed p value of <0.05 was considered statistically significant.

Table 1: Baseline characteristics of patients with stroke and non-cerebral thromboembolism

	Stroke N:213	Non-cerebral thromboembolism N:115	p value
Age, years mean±sd	75,7±10	73,4±12,8	0,073
Gender, Female, n(%)	135 (63%)	61 (53%)	0,069
Hypertension n(%)	156 (73%)	91 (79%)	0,238
Diabetes Mellitus n(%)	71 (33%)	50 (43%)	0,069
Coronary artery disease n(%)	81 (38%)	60 (52%)	0,014
Peripheral artery disease n(%)	13 (6%)	12 (10%)	0,158
Chronic renal failure n(%)	21 (10%)	18 (16%)	0,122
Heart Failure n(%)	64 (30%)	29 (25%)	0,354
Hyperlipidemia n(%)	43 (20%)	41 (36%)	<0.001
Prior stroke n(%)	37 (17%)	13 (11%)	0,145
Prior transient ischemic attack n(%)	11 (5%)	18 (16%)	0,001
Prior non-cerebral embolic event n(%)	6 (3%)	21 (18%)	<0,001
Warfain use n(%)	30 (14%)	63 (55%)	<0.001
INR>2	4 (13%)	13(21%)	0,394
NOAC use n(%)	33 (15%)	8 (7%)	0,026
Antiagregan use n(%)	85 (40%)	65(56%)	0,004
CHA_2DS_2-VASc score median (IQR), mean±sd	5 (0-9) 4,52±1,66	5 (0-9) 4,29±2,02	0,196
CHAD-VASc Score, n(%)			
0	3 (1,4%)	1(0,9%)	0,671
1-3	53 (25%)	39 (34%)	0,082
4-6	131 (61%)	58 (50%)	0,053
7 and more	26 (12%)	17 (15%)	0,510
Hospital mortality n(%)	40 (19%)	20 (17%)	0,756

CHA_2DS_2-VASc : [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)] INR: International normalization ratio, NOAC: Non-vitamin K antagonist oral anticoagulants N: number,Sd:standart deviation

Results

Demographic and clinical features of the patients are presented in [Table 1]. The mean age (75.7±10 years vs. 73.4±12.8 years, p=0.073) and gender distribution (females, 63% vs. 53%, p=0.069) were similar in the stroke and non-cerebral embolism groups. The rates of hypertension, diabetes mellitus, chronic renal failure, peripheral arterial disease, heart failure, and in-hospital mortality were comparable between the groups (p<0.05). However, the rates of coronary artery disease and hyperlipidemia were higher in the non-cerebral embolism group (p<0.05).

Although the rate of prior stroke was comparable between the stroke and non-cerebral embolism groups, the rates of prior transient ischemic attack and prior non-cerebral embolism before the last incident were higher in the non-cerebral embolism group (p<0.05). Prior NOAC use was higher in the stroke group, whereas antiplatelet and warfarin use was more common in the non-cerebral embolism group (p<0.05). International normalization ratio (INR) value was above 2 in 13% of patients that received warfarin therapy before the index event in the stroke group, and this rate was 21% in the non-cerebral embolism group. The difference between the groups was not statistically significant (p=0.394).

The median and mean CHA_2DS_2-VASc score was similar between

stroke and non-cerebral embolism group (median(min-max): 5(0-9), mean±sd: 4.52±1.66 vs. 4.29±2.02, p=0.013). When grouping the patients according to the CHA_2DS_2-VASc score, the number of patients with a score of 1 to 3 points, number of patients with a score of 4 to 6 points and number of patients with a score of 7 points and above were comparable between the stroke and non-cerebral embolism groups (p>0.05).

In the non-cerebral embolism group, 63% had lower extremity embolism, 29% had upper extremity embolism, 5% had mesenteric embolism, 2% had both right and left lower extremity embolism, and 2% had both upper and lower extremity embolism [Figure 1]. The mean CHA_2DS_2-VASc score, rates of medical and surgical therapy, and prior antiplatelet and anticoagulant use were comparable when grouping the patients according to anatomic localization of non-cerebral embolism. However, there was a significant difference between all groups with respect to mortality according to the anatomic localization of embolism (p<0.05).

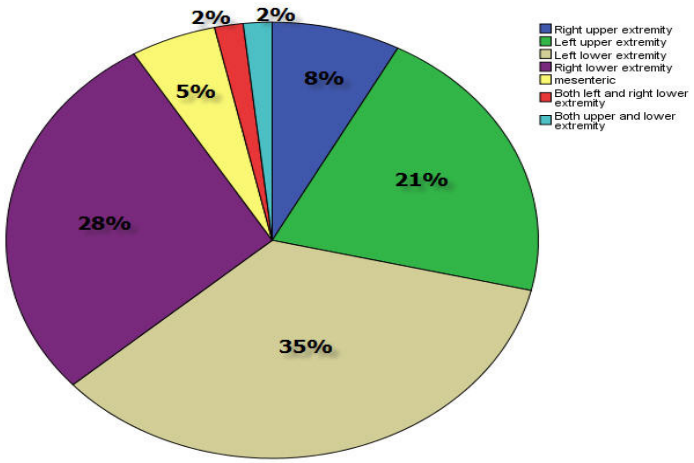

Figure 1: Anatomic distribution of non-serebral embolic events

Discussion

This study compared the thromboembolic risk level based on CHA_2DS_2-VASc score before the index event and in hospital mortality between NVAF patients suffering stroke and non-cerebral arterial thromboembolism. CHA_2DS_2-VASc score and in hospital mortality was not different between NVAF patients with stroke and non-cerebral thromboembolism.

Thromboembolic events associated with AF have been one of the most important factors determining prognosis [5]. The studies have therefore aimed at developing a risk-stratification method and $CHADS_2$ score [cardiac failure, hypertension, age, diabetes, stroke (doubled)] has been the first scoring system developed for this purpose [10]. Yamamato et al. has been the first to evaluate the value of $CHADS_2$ score in predicting non-cerebral embolic events. $CHADS_2$ score was found to be unreliable in predicting non-cerebral embolic events. The most important limitation of their study was that the data of stroke patients were obtained from other studies [13].

CHA^2DS^2-VASc score has been proposed with the addition of certain risk factors for thromboembolism such as female gender, vascular disease, and age at or above 65 years to the $CHADS^2$ score, and this extended scoring system has been introduced into the practice in many countries [14]. Bekwelem et al. performed a meta-analysis of studies on patients with NVAF receiving anticoagulant and antiplatelet drugs, and they reported the incidence, risk factors and consequences of extracranial embolism. The analysis of these data showed comparable CHA_2DS_2-VASc scores in patients with stroke and those sustaining extracranial embolism [15]. However, all patients in this analysis set had received antiplatelet or oral anticoagulant drugs as this meta-analysis reviewed previous phase 3 and phase 4 studies. Therefore, their data do not reflect real world situation. The present study directly compared CHA_2DS_2-VASc scores between NVAF patients with stroke and non-cerebral embolism. CHA_2DS_2-VASc score was similar between two groups. Another remarkable finding was that factors constituting the CHA_2DS_2-VASc score were not identical in the two groups. For instance, history of coronary artery disease was more common in patients with non-cerebral embolism. Actual cause of this finding is unknown; however, higher prevalence of certain risk factors such as hypertension, hyperlipidemia, diabetes, and chronic renal failure in patients with non-cerebral embolism might have contributed to this finding.

Another remarkable finding of the present study was higher prevalence of transient ischemic attack and previous non-cerebral embolism in patients with non-cerebral thromboembolism. Although actual cause has not been clearly identified, some factors have been associated with this finding. One of these factors is high caliber of peripheral arteries, and thus, size of the embolus must be large enough to produce clinical symptoms of acute embolism. It was considered that due to large size of embolus in patients with non-cerebral embolism, detection rates of clinical stroke and non-cerebral embolism were higher in these patients. Prospective clinical studies are required to confirm this theory.

The second factor is that the mechanism of thrombus formation can be different in stroke patients and patients with non-cerebral embolism. Stroke and transient ischemic attack can be associated with non-thromboembolic factors such as thrombosis or plaque embolization in the intracranial arteries. Other atrial factors in addition to AF such as endothelial dysfunction, fibrosis, impaired myocyte function, chamber dilatation and mechanical dysfunction in the left atrial appendage even may cause stroke independently[16].

Although we meticulously selected the patients with non-cerebral thromboembolism embolism as defined in methods section. Peripheral arterial occlusion might be resulted from aterothrombosis instead of thromboembolism due to higher rate of coronary artery disease and hyperlipidemia in the non-cerebral thromboembolism group.

It is not known as how this factor varies in the two groups. It is however clearly known that oral anticoagulation is indicated in NVAF patients with transient ischemic attack or stroke independent of the pathophysiology . The third factor is that the use of oral anticoagulant therapy is less satisfactory in patients with non-cerebral embolism. Although the use of antiplatelet drugs is more common in patients experiencing non-cerebral embolic events, anti-platelet therapy is known to be less protective against thromboembolism. Warfarin use is more common in patients with non-cerebral embolism; however, number of patients achieving therapeutic targets is lower. More common NOAC use in stroke patients might have protected these patients against extracranial embolism. Beklewen et al. reported that NOAC use was associated with a 30% further decrease in the risk of extracranial embolism compared with the risk of stroke [15]. This finding is supports the finding of the current study.

In the present study, the majority of the patients (95%) experienced

Table 2: Characteristics of patients according to location of embolism

	Upper extremityα N:33	Lower extremityα* N:74	Mesenteric N:6	p
CHA_2DS_2-VASc score mean±sd	3,90±2,02	4,5±1,97	4,83±2,14	0,306
Surgical or endovascular procedure during hospitalization n(%)	24 (73%)	48 (65%)	6 (%100)	0,173
Hospitalization without surgical or endovascular procedure n(%)	9 (27%)	26 (35%)	0 (0%)	0,173
Prior oral anticoagulation use n(%)	19 (58%)	49 (66%)	2 (33%)	0,232
Prior antiaggregan use n(%)	20 (61%)	40 (54%)	4 (67%)	0,719
Hospital mortality n(%)	4 (12%)	12 (16%)	4 (67%)	0,005

αtwo patients had both upper and lower extremity embolism who are not included
*Two patients have bilateral lower extremity embolism included in lower extremity group.
CHAD-VASc : [congestive heart failure / left ventricular dysfunction, hypertension, age≥75 years (doubled), diabetes, stroke (doubled) – vascular disease, 65–74 years of age, and sex category (female)]
N:number

extremity embolization while a small portion (5%) experienced mesenteric embolization. These data are close to those reported by Abbott et al. [17] in a series of cases from the US (83% vs. 8%), while these data were different than reported in the study by Frost et al. (60% vs. 40%) [18]. The prevalence of mesenteric embolism might have been underestimated for being difficult to remember this condition in the diagnosis, frequently remaining overlooked or misdiagnosed [19]. On the other hand, it was suggested that splenic embolisms result in insignificant clinical consequences and renal embolisms become symptomatic and manifest clinical signs in late periods, and this explains why such visceral embolisms are underreported [20]. Mortality rate was comparable in the stroke (19%) and non-cerebral embolism (17%) groups. Mortality rate in patients with upper and lower extremity embolism was lower than stroke patients; however, mortality rate in patients with mesenteric embolism was higher than in stroke patients, despite CHA_2DS_2-VASc score in mesenteric embolism group was not different than the score of stroke patients. According to our findings, the differences in mortality in patients with stroke and non-cerebral embolism were due to the localization of embolism rather than thromboembolic risk level. Durability to ischemia and clinical consequences are different between affected organs. Extremites are more durable to ischemia and clinical outcomes are more tolerable comparing to stroke. In patients with mesenteric embolism, operational procedure more complex and clinical risk level (late admission, difficult to diagnose) is higher than the patients with upper and lower extremity embolism.

Study Limitations

Since the data of the present study are based on retrospective review of hospital records, some data may be missing or inaccurately recorded. Low rate of visceral embolism due to misdiagnosed or undiagnosed patients associated with difficulties in diagnosing mesenteric, renal and splenic embolism might have biased the study findings. On the other hand, some patients with non-cerebral embolism may have remained asymptomatic due to small size of the embolism, and this may have caused that some patients with non-cerebral embolism may have not examined objectively.

Conclusions

Among patients with NVAF CHA_2DS_2-VASc score was similar between stroke and non-cerebral thromboembolism. In addition mortality rate was comparable between the two groups. However the parameters constituting the CHA_2DS_2-VASc score were not identical for stroke and non-cerebral embolism groups. The prevalence of non-cerebral embolism was higher in patients with a previous history of transient ischemic attack and non-cerebral embolism. For this reason, predicting non-cerebral embolism requires development of a different scoring system to predict thromboembolism.

Conflict Of Interests

None.

Disclosures

None.

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