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Von Willebrand factor and ADAMTS13 plasma in older patients with high CHA2DS2-VASc Score with and without atrial fibrillation

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Abstract. – OBJECTIVE: Ischemic stroke risk rises with the increasing cardiovascular risk factors in patients with and without AF. How atrial fibrillation (AF) incrementally contributes to the risk for ischemic stroke with increasing age and multiple cardiovascular risk factors is unclear. Von Willebrand factor (vWF) is a biomarker of endothelial dysfunction.

PATIENTS AND METHODS: We suggested that in older patients with high CHA2DS2-VASc Score, the vWF and ADAMTS13 would be comparable between patients with and without AF. Consecutive 196 old patients (≥ 60 years, 45.9% with concomitant AF) with and without non-valve atrial fibrillation were recruited from April 2014 to April 2016. Data on baseline clinical characteristics were recorded at study entry. Plasma ADAMTS13 levels and plasma vWF levels were determined. Statistical analyses were performed using SPSS19.0 statistical software package.

RESULTS: There were significant correlations between plasma vWf levels, ADMATS13 and CHA2DS2- VASc Score in older patients with and without AF (with AF: Spearman, r = 0.215, $p < 0.05$; without AF: Spearman, r = 0.197, $p < 0.05$). Results of research indices in our older patients were as follows: vWf 180. 79 ± 28.27 IU/dL in AF and 153.5 ± 35.54 in non AF with $p < 0.001$, ADAMTS13 431.5 ± 160.33 IU/dL in AF and 536.7 ± 169.96 in non AF with $p < 0.05$. Results of research indices in our older patients (≥ 75 year) were as follows: vWf 181.4 ± 22.04 in AF and 174.1 ± 29.45 in non AF, and ADMATS-13 412.9 ± 130.76 IU/dL in AF and 451.7 ± 153.18 in non AF. There were no differences ($p > 0.05$). CHA2DS2-VASc Score can predict stroke risk in old patients without atrial fibrillation. At high CHA2DS2-VASc Score, the levels of vWF and ADAMTS13 have difference in old patients (60-74) with and without AF, but in such older patients, age (≥ 75 year), there were no differences. In elderly patients, atrial fibrillation has a limited effect on VWF, and the age is an important factor affecting the endothelial function.

CONCLUSIONS: For elderly patients with a high incidence rate of stroke and thrombosis, we should pay more attention to the thrombotic events, and atrial fibrillation can be used as one of the risk factors involved and improving the risk scoring system of stroke.

Key Words:
Atrial fibrillation, CHA2DS2-VASc, Vwf, Old patients, Ischemic stroke.

Introduction

Atrial Fibrillation (AF) is the most common cardiac arrhythmia of clinical significance[1], affecting 1% to 1.5% of the population in the developed world. Arial fibrillation confers a five-fold increased risk of stroke, and 1/5 of all strokes are attributed to this arrhythmia[2].

Simple clinical risk scores have been useful in patients with AF, for example, the CHA2DS2-VASc Score (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes mellitus, stroke/transient ischemic attack/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65-74 years, sex category [female]), which are recommended in current guidelines (based on possible points, with higher scores indicating higher risks)[3,4]. Ischemic stroke risk rises with the increasing of cardiovascular risk factors in patients with and without AF. In recent years, the CHA2DS2-VASc Score is recognized as a cluster of multiple risk factors increasing the risk of ischemic stroke, TE, and death, whether or not AF is present[5,6]. How atrial fibrillation (AF) incrementally contributes to the risk for ischemic stroke with increasing age and multiple cardiovascular risk factors is unclear. Thus, we suggested that the CHA2DS2-VASc Score could predict ischemic stroke, TE, and death in old patients wi-

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thout AF in a manner comparable with that evident in AF populations.

The mechanisms behind cerebral thrombo-embolism in AF are not completely understood, but it is well documented that AF is associated with a prothrombotic state, demonstrated by higher levels of von Willebrand Factor (vWF), when compared to health control subjects[7,8]. von Willebrand Factor (vWF), the only known substrate for a disintegrin and metalloproteinase with thrombospondin type 1 motif-13 (ADAMTS13), has been proposed as a biomarker of endothelial damage/dysfunction. Circulating plasma vWF is almost mainly synthesized, stored and secreted by endothelial cells in response to endothelial activation or damage[9]. It is a multimeric glycoprotein, an enormous size (> 20*106 Daltons) that plays a crucial role in platelet adhesion and aggregation, which are the main initial steps in hemostasis. The synthetic process is as follows: vWF undergoes dimerization and multimerization first; then, it is proteolyzed by ADAMTS13 protease into functional vWF multimers of varying size[10,11].

Low plasma ADMATS13 is a useful predictor for cardiac and cerebrovascular events in coronary artery diseases[12,13]. In atrial fibrillation, ADMATS13 level in patients after treatment with cardio conversion is useful for prediction of recurrence of AF[14]. Blood stasis has been shown to down regulate ADAMTS13 activity[15]. We hypothesized that in older patients with high CHA2DS2-VASc Scores, the vWF and ADAMTS13 would be comparable between patients with and without AF.

Patients and Methods

Patients

We recruited consecutive 196 old patients (≥ 60 years) with and without non-valve atrial fibrillation from 2014.4-2016.4. This study was approved by the Ethics Committee of Beijing Chao-Yang Hospital. Signed written informed consents were obtained from all participants before the study. AF was identified by a 12-lead ECG. We excluded patients with valvular AF or prosthetic heart valves, as well as those with recent (< 3 months) venous or systemic thromboembolism, any acute coronary syndrome, stroke, a prior diagnosis of cancer and chronic obstructive pulmonary disease, hemodynamic instability, infection or inflammatory disease, hospital or surgical interventions in the preceding 6 months.

Data on baseline clinical characteristics were recorded at study entry. The CHA2DS2-VASc was calculated using established definitions of the different risk factors, as previously described.

Blood Sampled and Laboratory Analysis

At study inclusion, blood samples were drawn traumatically and without stasis into syringes pre-loaded with EDTA. Platelet-poor plasma fractions were obtained by centrifugation at 4°C for 10 min at 3000 g. Aliquots were stored at -80°C to allow batch analysis.

Plasma vWF levels were determined using ab108918 von Willebrand Factor Antigen human ELISA kits (EU and ROW, London, UK) according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation were 5.0% and 9.7%, and the lower limits of detection were 1.1 mu/mL.

Plasma ADAMTS13 levels were determined using the l mu bind ADAMTS13 enzyme linked immunosorbent assay (ELISA) kit (RD, Cambridge, MA, USA) according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variation were 3.7% and 5.7%, and the lower limits of detection were 0.01-0.26 ng/mL. All laboratory work was done in a blinded manner to the patient's details.

Statistical Analysis

Statistical analyses were performed using SPSS19.0 (Version X; IBM, Armonk, NY, USA) statistical software package. Continuous variables are presented as a mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables, as percentages. Correlations were performed using Spearman's rank correlation method. A two-side probability value of $p < 0.05$ was considered statistically significant.

Results

We included 196 older patients with and without non-valvular AF. Baseline characteristics of the patients are shown in Table I. There were significant correlations between plasma vWf levels and CHA2DS2- VASc risk Score in older patients with and without AF (with AF: Spearman, r = 0.215, $p < 0.05$; without AF: Spearman, r = 0.197, p < 0.05). Aspirin did not take any influence (Table II). There were significant correlations between ADMATs13 plasma levels and CHA2DS2- VASc risk Score in older patients with AF (AF: Spearman, r = -0.255, $p < 0.05$); and on difference were found in patients without AF: Spearman, r =

Table I. Baseline characteristics of patients with and without atrial fibrillation.

	No. (%) of patients			
Clinical Characteristics	**With atrial fibrillation (no. = 90)**	**Without atrial fibrillation (no. = 106)**	**X**	***p***
Male	42 (46.7)	52 (49.1)	0.111	0.739
Age	72.11±7.62	70.31±5.87	55.789	0.000
60-74	46 (51.1)	70 (66.0)		
≥ 75	44 (48.9)	36 (34.0)		
Baseline comorbidity				
Hypertension	68 (75.6)	84 (79.2)	0.381	0.537
Previous thromboembolism	12 (13.3)	18 (17.0)	0.5	0.48
Vascular disease	14 (15.6)	22 (20.8)	0.878	0.349
Congestive heart failure	68 (75.6)	34 (32.1)	36.896	0.000
Diabetes mellitus	24 (26.7)	32 (30.2)	0.296	0.586
Previous ischemic stroke	42 (46.7)	30 (28.3)	7.064	0.008
Renal disease	6 (6.7)	34 (32.1)	2.840	0.092
Hyperthyroidism	4 (4.4)	6 (5.7)	0.249	0.700
Baseline medications				
Loop diuretics	34 (37.8)	44 (41.5)		0.266
ACEI	42 (46.7)	50 (47.2)		0.460
B-blockers	42 (46.7)	38 (35.8)		0.330
Statins	72 (80.0)	80 (75.5)		0.557
CC antagonists	10 (11.1)	10 (9.4)		0.522
Aspirin	56 (62.2)	82 (77.4)		0.000
CHA2DS2-VASc Score				
3-4	38 (42.2)	68 (64.2)		
≥5	52 (57.8)	38 (35.8)		

Table II. Correlation between the CHA2DS2- VASc Score and plasma von Willebrand factor levels in older patients with and without non-valvular AF

	Spearman r	*p*
All patients	0.217	0.002
With atrial fibrillation	0.215	0.042
Without atrial fibrillation	0.197	0.043

Table III. Correlation between the CHA2DS2- VASc Score and plasma ADMATs13 levels in older patients with and without non-valvular AF.

	Spearman r	*p*
All patients	-0.234	0.001
With atrial fibrillation	-0.255	0.015
Without atrial fibrillation	-0.165	0.092

Table IV. Difference between vWF levels and plasma ADMATs13 levels in older patients with and without non-valvular AF AF (NVAF).

	With atrial fibrillation	Without atrial fibrillation	*t*	*p*
vWF levels (UI/dL)	180.79±28.27	153.5±35.54	5.813	0.000
ADMATS-13 (ng/ml)	431.5±160.33	536.7±169.96	-4.335	0.015

-0.165, $p > 0.05$. Aspirin did not take any influence. There was negative correlation between vWf and ADMATs13 (Spearman, r = -0.732, $p = 0.000$) (Table III).

Results of research indices in our older patients were as follows: vWf 180.79 ± 28.27 IU/dL in AF and 153.5 ± 35.54 in non AF, $p < 0.001$, ADMATS-13 431.5 ± 160.33 IU/dL in AF and 536.7 ± 169.96 in non AF, $p < 0.05$. There were no differences between patients taking aspirin, warfarin or not (Table IV).

In this study, results of research indices in our older patients (60-74 ages) were as follows: vWf 172.57 ± 22.04 in AF and 145.68 ± 35.17 in non

Table V. At different ages, vWF levels and plasma ADMATs13 levels in older patients with and without non-valvular AF (NVAF).

		With atrial fibrillation	Without atrial fibrillation	*t*	*p*
60-74	vWF levels (UI/dL)	172.57±22.04	145.68±35.17	6.108	0.000
	ADMATS-13 (ng/ml)	451.4±179.28	563.7±159.65	-3.527	0.001
≥75	vWF levels (UI/dL)	181.4±22.04	174.1±29.45	1.218	0.227
	ADMATS-13 (ng/ml)	412.9±130.76	451.7±153.18	-1.237	0.220

AF with $p < 0.001$, ADMATS-13 451.4 ± 179.28 IU/dL in AF and 563.7 ± 159.65 in non AF with $p < 0.05$. Results of research indices in our older patients (≥ 75 ages) were as follows: vWf 181.4 ± 22.04 in AF and 174.1 ± 29.45 in non AF, and ADMATS-13 412.9 ± 130.76 IU/dL in AF and 451.7±153.18 in non AF. There were no differences ($p > 0.05$) (Table V).

Discussion

In this "real world" cohort study, our principal findings were that (1) CHA2DS2-VASc Score can predict stroke risk in old patients without atrial fibrillation; (2) at high CHA2DS2-VASc Score, the levels of vWF and ADAMTS13 have difference in old patients (60-74) with and without AF, but in such older patients, there was no difference in age (≥ 75year). There were no differences between patients taking aspirin, warfarin or not, where vWF levels were very similar before and after treatment with warfarin (difference not statistically significant). In our study, we exclude warfarin[16].

From Table II, vWf was independently associated with CHA2DS2-VASc Score for stroke in AF ($p < 0.05$), and vWf was independently associated with CHA2DS2-VASc Score for stroke in non AF ($p < 0.05$), raised vWf levels were predictive for subsequent stroke and vascular events[17]. CHA2DS2-VASc Score can be used to predict the outcome of ischemic stroke in old patients with non-valve AF. A study found CHA2DS2-VASc Scores have limitations in predicting the 1-year prognosis of stroke/TIA patients with NVAF. Because most of the study population suffered atherosclerosis stroke, this study suggested that CHA2DS2-VASc Scores might be more applicable to risk prediction in patients with cardioembolic stroke[18]. This risk stratification system may predict the risk of atherosclerosis stroke[19]. In recent years, the use of CHA2DS2-VASc Score in predicting ischemic stroke, TE, and death has extended beyond the original disease stage for which it was proposed[5-6]. For example, Poci et al[20] reported that the CHA2DS2-VASc Score in patients with acute coronary syndrome without AF is significantly associated with all-cause mortality. Thus, CHA2DS2-VASc Score was a cluster of multiple risk factors, which was helpful for the early prevention and treatment of some endpoints, including stroke and all-cause death whatever patients with or without atrial fibrillation. Also, this study suggests that future studies may be warranted to investigate whether these high-risk non-AF patients could benefit from thromboprophylactic therapy. We hope these findings will help to promote an open and meaningful dialog about the management of potential thrombotic risk.

In this study, from Table IV, we find vWF in older patient with AF was higher than that in older patient without AF ($p < 0.05$). The ADMATS level was lower than that in non-AF patients ($p < 0.05$). The importance of vWF to cardiovascular disorders has been long recognized[21]. Raised levels of vWF have been described in AF individuals, compared to those in sinus rhythm[22]. VWF levels in AF patients are not altered by warfarin treatment[16]. Also, the prognostic role of plasma vWF in AF has been well-established[23,24]. After the correction of heart failure and age, the risk of atrial fibrillation will be increased by 0.084 times with the increase of vWF levels by 1 μl/ dL ($p < 0.05$). From Table V, we found that in patients aged 60-74 years old, the level of VWF in patients with atrial fibrillation was higher than that in patients with non-atrial fibrillation ($p < 0.05$), but the level of ADMATS was lower than that in patients with non-atrial fibrillation ($p < 0.05$). In patients aged ≥ 75 years old, the level of VWF in patients with atrial fibrillation was still higher than that in patients with non-atrial fibrillation, but the level of ADMATS was lower than that in patients with non-atrial fibrillation, and the differences were not statistically significant. Therefore, for elderly patients, the impacts of atrial fibrillation on VWF and ADMATS13 were decreased compared with those in younger patients, and atrial

fibrillation was one of the factors, rather than the necessary condition, affecting the level of VWF and ADMATS13, and age was an important factor affecting the endothelial function. Krishnamoorthy et al[25] suggested that patients with HF without AF had a similar risk for thromboembolic events when compared to the patients with persistent AF. At the same time, Guo et al[26] found that, if elderly and with multiple risk factors, non-AF patients may have a risk of incident ischemic stroke comparable or even higher than patients with AF. These studies suggested that AF is only a risk factor to predict stroke and thromboembolic events. Of course, the definitions for these study endpoint and patients may slightly differ. The risk of ischemic stroke/TIA and death among elderly non-AF patients increases substantially in the presence of high scores, highlighting potentially unmet medical needs. In the Rotterdam Study, which included more than 6000 participants, the risk of stroke was associated with vWF levels in the general population, no matter AF was present or not[27]. At the same time, García-Fernández et al[28] demonstrated that raised vWF levels doubled the risk of stroke, cardiovascular death and major bleeding, and increased (by more than 50%) cardiovascular events and all-cause mortality. Therefore, for the elderly patients with a high incidence rate of stroke and thrombosis, we should pay more attention to the thrombotic events, and establish a more perfect scoring system to identify not only patients with atrial fibrillation, but also risk groups of stroke.

There are several limitations in this study. Firstly, the diagnosis of non-valvular atrial fibrillation (NVAF) may have been suboptimal, as paroxysmal AF is more difficult to detect and the diagnosis can be easily missed relying only on self-reporting and a single ECG. Other studies found that paroxysmal AF occurred more often than persistent AF in stroke/TIA patients[29,30]. Secondly, the risk was not distinguished in our study. Previous research suggested that patients with HF without AF had a similar risk for thromboembolic events when compared to the patients with persistent AF[25]. Thirdly, the number of patients was small, and it was important for advanced study.

Conclusions

We suggest that, in China, the CHA2DS2-VASc Score can predict the outcome of the ischemic stroke /TIA of older patients with NVAF and without NVAF, which can help to predict the risk in old patients. VWF, as a biomarker of endothelial function, was independent risk factor for stroke. Perhaps descending the level of vWF can descend the risk of endpoint; this is the next aim of our study. In elderly patients, atrial fibrillation has a limited effect on VWF. For elderly patients with a high incidence rate of stroke and thrombosis, we should pay more attention to the thrombotic events and establish a stroke scoring system suitable for elderly patients to better identify the risk groups of stroke; besides, atrial fibrillation can be used as one of the risk factors involved, improving the risk scoring system of stroke.

Conflict of interest

The authors declare no conflicts of interest.

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